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(54) Title: CHIRAL LIGANDS, TRANSITION-METAL COMPLEXES THEREOF AND USES THEREOF IN ASYMMETRIC REACTIONS

(57) Abstract: Chiral ligands and transition metal complexes based on such chiral ligands useful in asymmetric catalysis are disclosed. The chiral ligands include phospholanes, P, N ligands, N, N ligands, biphenols, and chelating phosphines. The ferrocene-based irridium (*R,R*)-f-binaphane complex reduces imines to the corresponding amines with 95-99.6 % enantioselectivity and reduces β-substituted-α-arylenamides with 95 % enantioselectivity. The transition metal complexes of the chiral ligands are useful in asymmetric reactions such as asymmetric hydrogenation of imines, asymmetric hydride transfer reactions, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition and epoxidation reactions.

CHIRAL LIGANDS, TRANSITION-METAL COMPLEXES THEREOF AND USES THEREOF IN ASYMMETRIC REACTIONS

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The present invention relates to chiral ligands and transition metal complexes thereof that are useful in asymmetric reactions. More particularly, the present invention relates to chiral phospholanes, P,N ligands, N,N ligands, biphenols, and chelating phosphines and transition metal complexes thereof that are useful in asymmetric catalysis.

2. DESCRIPTION OF THE PRIOR ART

Discovery of new chiral ligands has been an essential element in the development of highly enantioselective transition metal-catalyzed reactions. New structural motifs play an important role in dictating enantioselectivities and reactivities of a reaction.

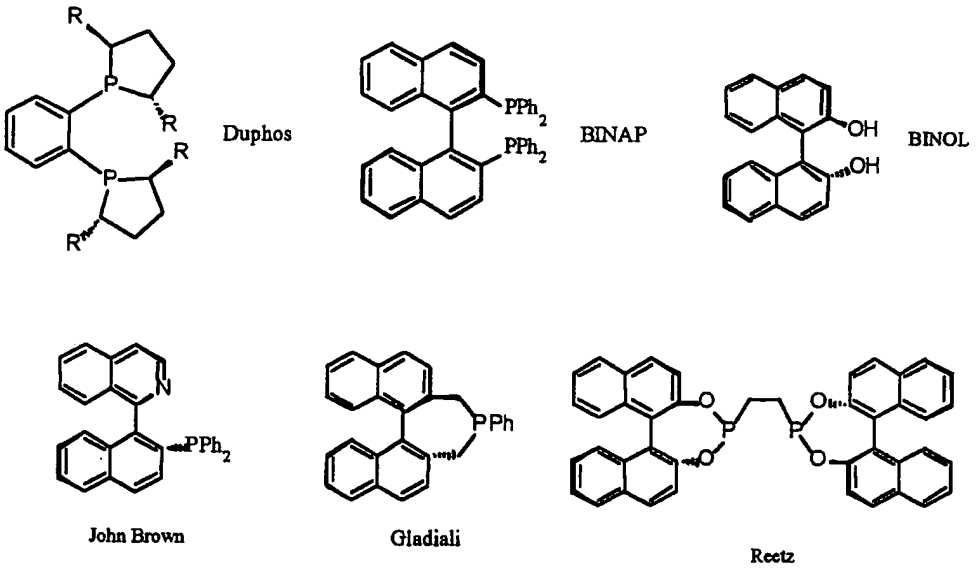
With the growing demand of enantiomerically pure compounds in pharmaceutical and agrochemical industry, asymmetric catalysis has become increasingly more important because of its high efficiency.

For example, biaryl atropisomeric ligands have been explored as effective ligand scaffolds for many asymmetric transformations. One of the most frequently used chiral chelating phosphines is BINAP (Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, 23, 345, Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, 120, 13529.).

Another family of excellent chiral phosphines is so called DuPhos (Burk, US patent 5,329,015, US Patent 5,202,493, US Patent 5,329,015, Burk, M, J. *J. Am. Chem. Soc.* **1991**, *113*, 8518, Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142), which has a rigid 1, 2-bis(phosphino)benzene backbone and electron-donating phospholane groups.

Gladiali et al. (Gladiali, S.; Dore, A.; Fabbri, D.; Lucchi, O. D.; Manassero, M. *Tetrahedron Asymmetry*, **1994**, 511.) made monodentate chiral phospholanes bearing the 1, 1'-binaphthyl framework. However the method for their synthesis is not feasible to make the corresponding chelating chiral phospholanes. Stelzer et al. (Bitterer, F.; Herd, O.; Kuhnel, M.; Stelzer, O.; Weferling, N.; Sheldrick, W. S.; Hahu, J.; Nagel, S.; Rosch, N. *Inorg. Chem.* **1998**, 37, 6408) only made racemic chelating phospholanes.

Reetz et al. prepared chelating chiral phosphinites using readily accessible binaphthanols as starting materials and demonstrated that they are excellent ligands for Rh-catalyzed asymmetric hydrogenation of dehydroaminoacids (Reetz, M. T.; Gosberg, A.; Goddard, R.; Kyung, S. *J. Chem. Soc., Chem. Commun.* **1998**, 2077). John Brown made a chiral phosphine and pyridine ligand with a biaryl chirality. Several related chiral ligands are shown in the Figure below.



While these ligands have been useful in a number of asymmetric reactions, there are still many more asymmetric transformations that can benefit from the discovery of new chiral ligands.

SUMMARY OF INVENTION

The present invention includes a ligand selected from the group consisting of compounds represented by A through K:

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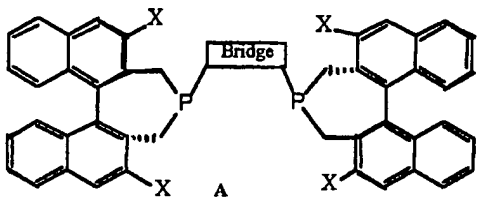
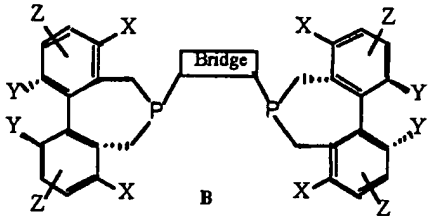
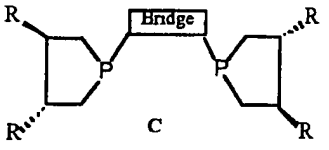
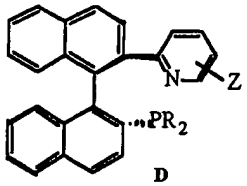
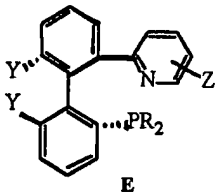
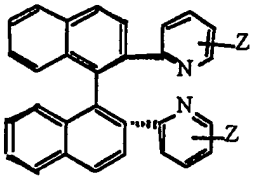


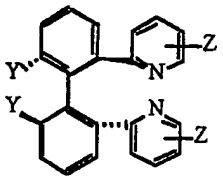


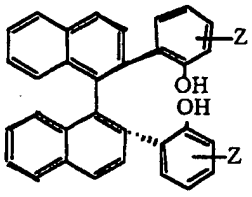


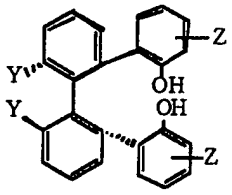


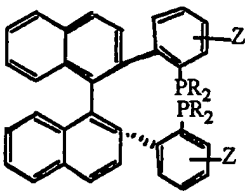


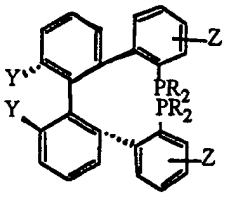












W

herein the bridge group is selected from the group

consisting of: $(CH_2)_n$ wherein n is an integer ranging from 1 to 8, $(CH_2)_nW(CH_2)_m$ wherein n and m are independently an integer ranging from 1 to 8 and W, wherein W is a divalent group selected from the group consisting of: 1,2-divalent phenyl, 2,2'-divalent 1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl, ferrocene, and a substituted derivative thereof; wherein each substituent in said substituted derivative is selected from the group consisting of: aryl, alkyl having 1-8 carbon atoms, F, Cl, Br, I, COOR, SO_3R, PR_3R_2, OR, SR, PR_2, AsR_2, SbR_2, aryloxyl, nitro, NR_2, vinyl, substituted vinyl and a combination thereof, wherein each R is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkaryl and aralkyl; wherein each X is independently selected from the group consisting of: hydrogen, halide, alkyl, aryl, alkoxy, silane, carboxylate and amide; each Y is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, carboxylate and amide; and each Z is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, amide, carboxylate, and a heterocyclic compound.

The present invention further includes a catalyst prepared by a process comprising contacting a transition metal salt, or a complex thereof, and a ligand selected from the group consisting of compounds represented by A through K as described above.

The present invention still further includes a process for preparation of an asymmetric compound using

a catalyst according to the present invention. The process comprises contacting a substrate capable of forming an asymmetric product by an asymmetric reaction and a catalyst prepared by a process comprising contacting a transition metal salt, or a complex thereof, and a ligand selected from compounds represented by A through K as described above.

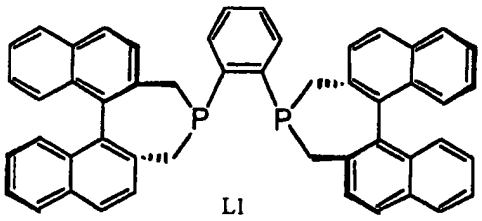
The ferrocene-based irridium (*R,R*)-f-binaphane complex reduces imines to the corresponding amines with 95-99.6% enantioselectivity and reduces β-substituted-α-arylenamides with 95% enantioselectivity.

DETAILED DESCRIPTION OF INVENTION

The present invention includes new phospholane ligands with mixed biaryl chirality. The P,N ligands, N,N ligands, biphenols and chelating phosphines are also derivatives of biaryl atropisomers. Also included are chiral five-membered ring phospholanes with stereogenic centers in 3,4 positions, phospholanes with a chiral biaryl atropisomer as the backbone and atropisomers of P,N ligands, N,N ligands, biphenols and chelating bisphophines. These chiral ligands can be used to facilitate a variety of metal-catalyzed asymmetric transformations. The bridge group can be $(CH_2)_n$ wherein n is an integer ranging from 1 to 8, $(CH_2)_nW(CH_2)_m$ wherein n and m are independently an integer ranging from 1 to 8 and W, wherein W is a divalent group selected from the group consisting of: 1,2-divalent phenyl, 2,2'-divalent 1,1'-biphenyl, 2,2'-divalent-1,1'-

binaphthyl, ferrocene, and a substituted derivative thereof. Each substituent in the substituted derivative can be aryl, alkyl having 1-8 carbon atoms, F, Cl, Br, I, COOR, SO_3R, PR_3R_2, OR, SR, PR_2, AsR_2, SbR_2, aryloxyl, nitro, NR_2, vinyl, substituted vinyl and a combination thereof and each R can independently be hydrogen, alkyl, aryl, alkaryl and aralkyl. Each X can independently be hydrogen, halide, alkyl, aryl, alkoxy, silane, carboxylate and amide, each Y can independently be hydrogen, alkyl, aryl, alkoxy, carboxylate and amide and each Z can independently be hydrogen, alkyl, aryl, alkoxy, amide, carboxylate, and a heterocyclic compound (i.e., a nitrogen, sulfur or oxygen heterocycle).

For each class of **A** to **K** ligands, the corresponding enantiomer, as well as enantiomeric mixtures, are also contemplated. **A** and **B** ligands are chelating chiral phospholanes with biaryl chirality in their backbone. **C** ligands have five-membered ring phospholanes with stereogenic centers in 3,4 positions. **D** and **E** are chiral P,N ligands with biaryl chirality. **F** and **G** are chiral N,N ligands with biaryl chirality. **H** and **I** are chiral biphenols with biaryl chirality. **J** and **K** are chiral phosphines with biaryl chirality. The preferred ligands of the present invention are selected from ligands designated A through K, which include members represented by the formula L1 through L56 depicted below:



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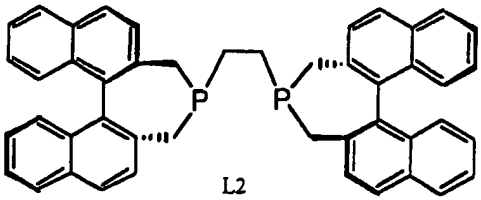

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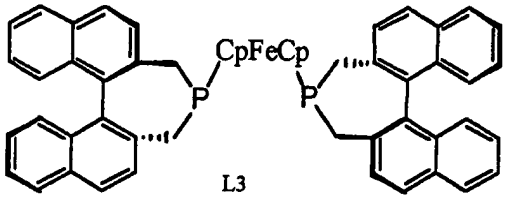

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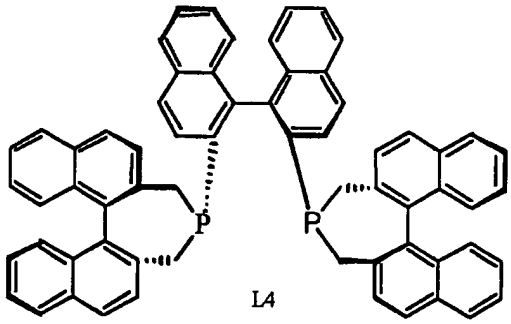

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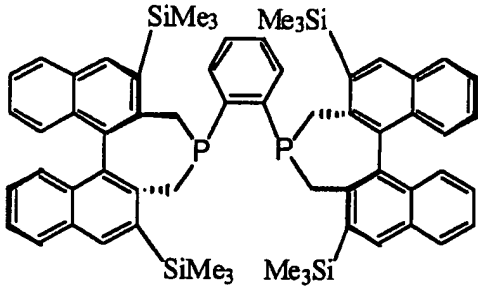

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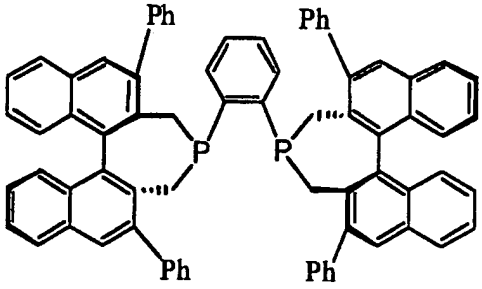

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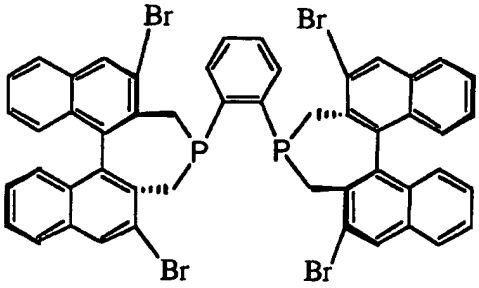

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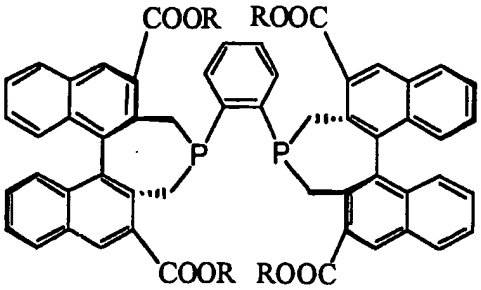

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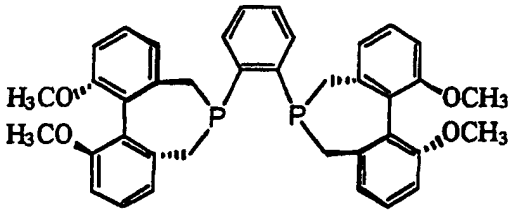

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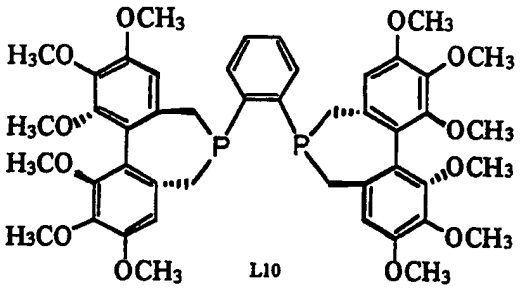

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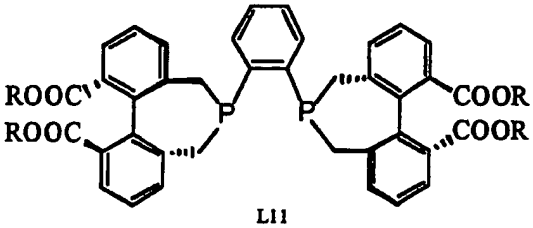

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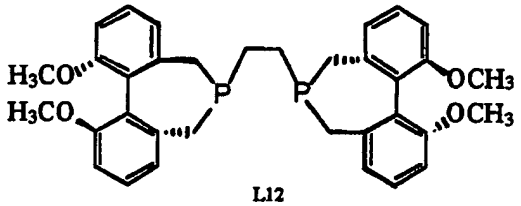

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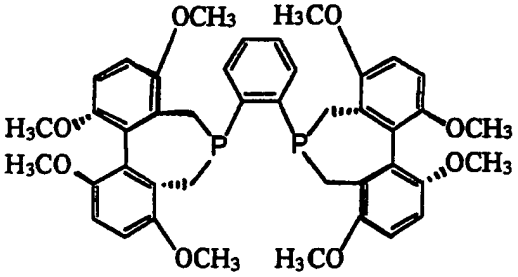

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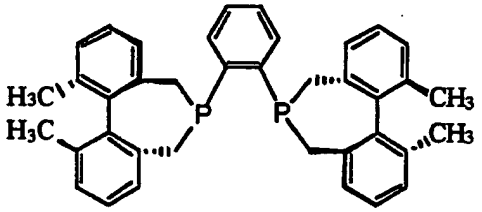

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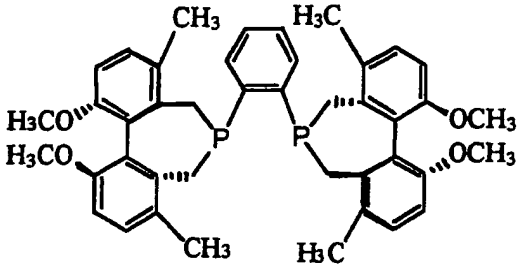

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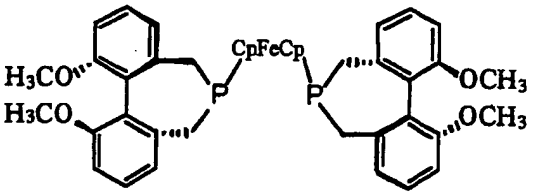

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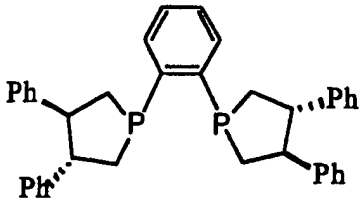

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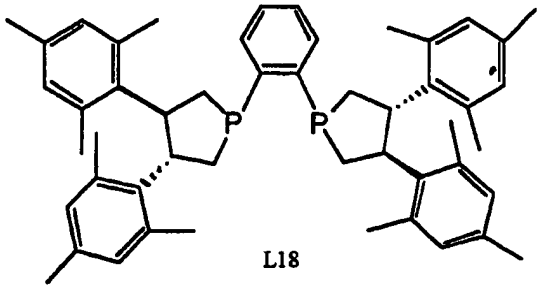

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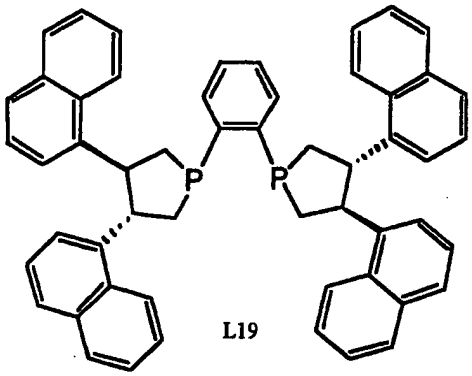

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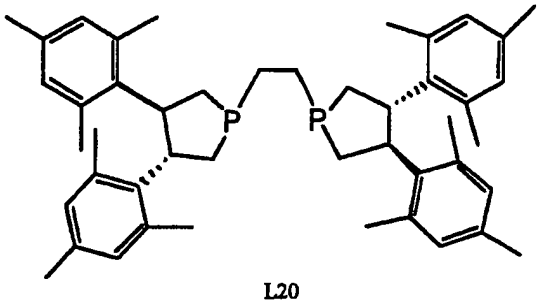

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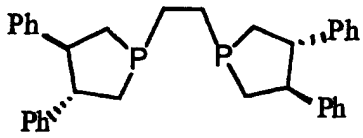

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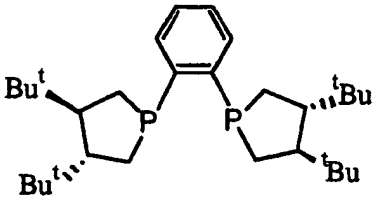

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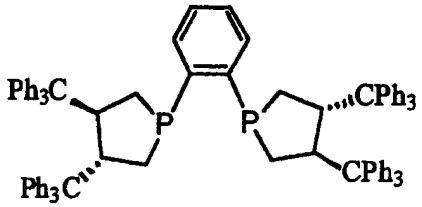

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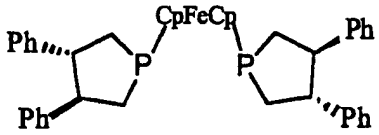

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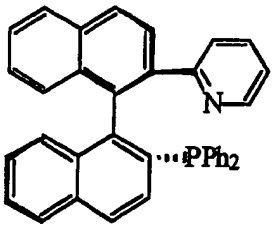

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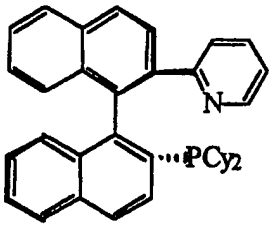

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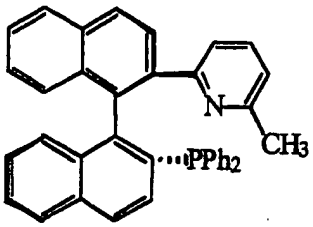

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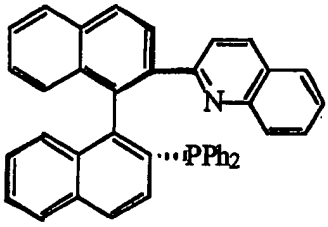

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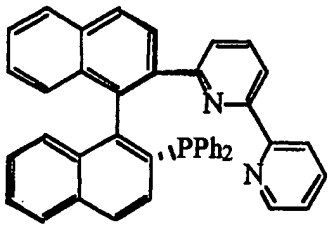

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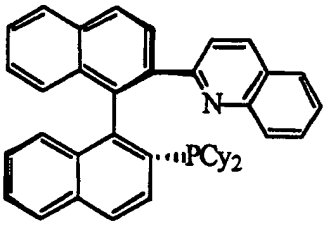

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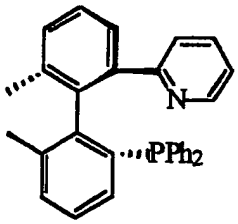

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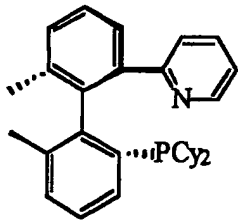

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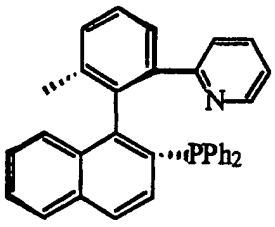

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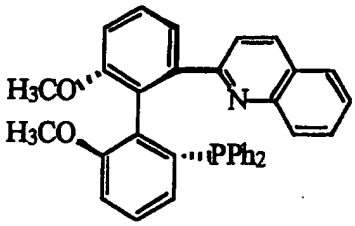

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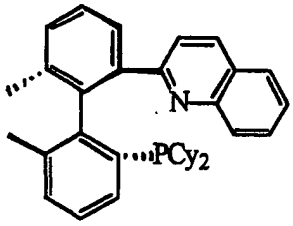

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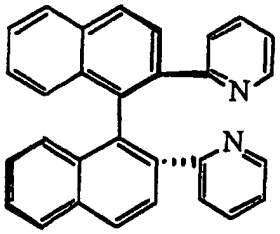

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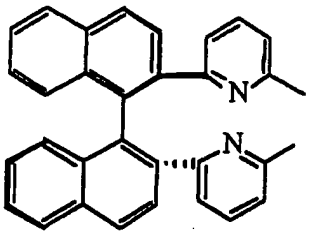

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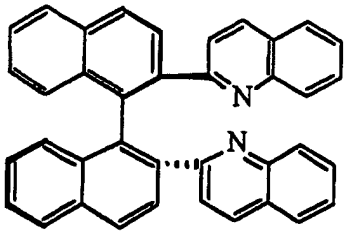

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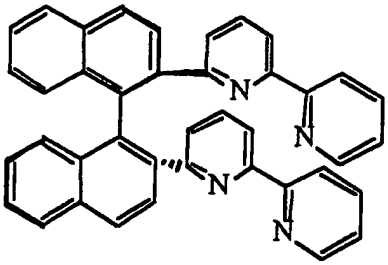

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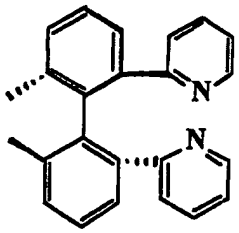

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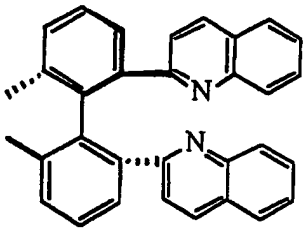

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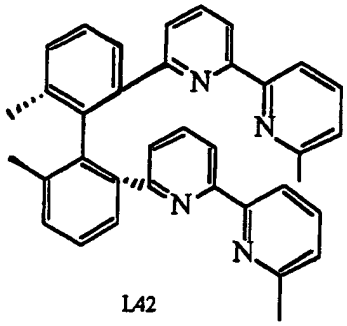

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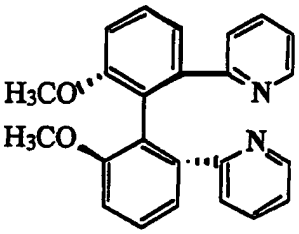

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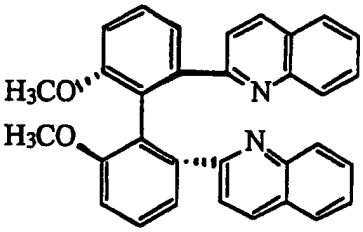

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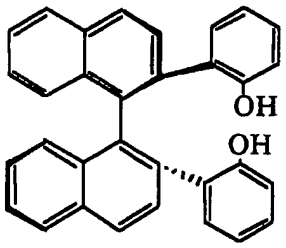

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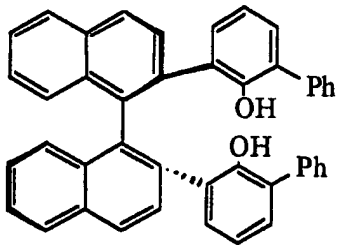

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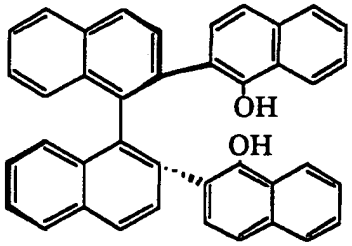

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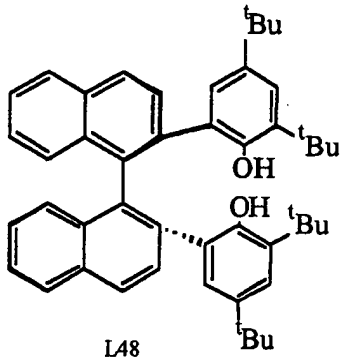

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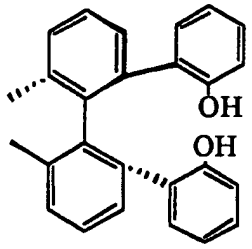

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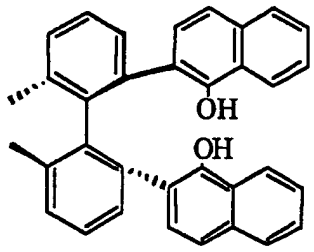
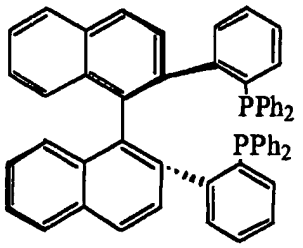
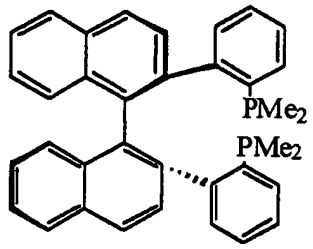


L50



L51



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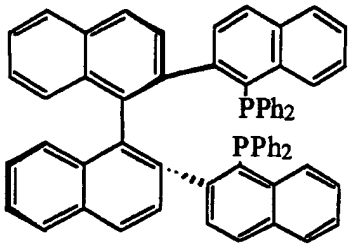

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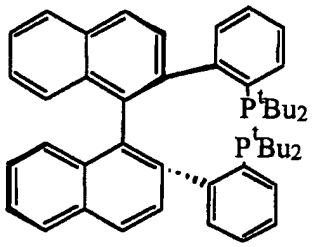

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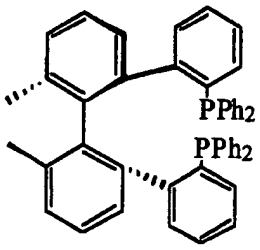
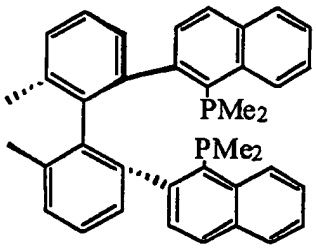


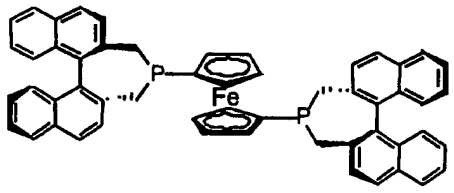
L55



L56

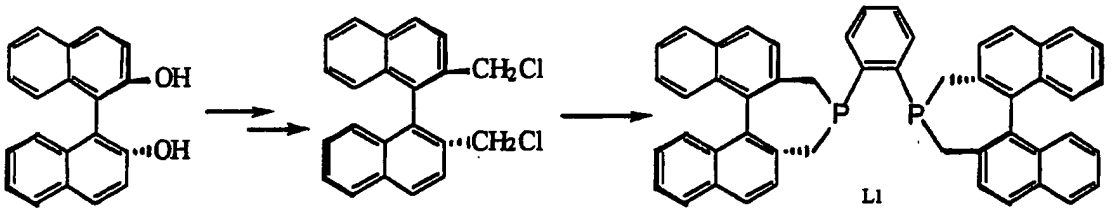
L1 to L8 are examples of A ligands. L9 to L16 are examples of B ligands. L17 to L24 are examples of C ligands. L25 to L35 are examples of D and E ligands. L36 to L44 are examples of F and G ligands. L45 to L50 are examples of F and G ligands. L51 to L56 are examples of J and K ligands.

f-Binaphane ligand and transition metal complexes thereof are preferred, irridium complexes of f-binaphane being the most preferred. The unsubstituted (*R,R*)-f-binaphane ligand is represented by the formula:



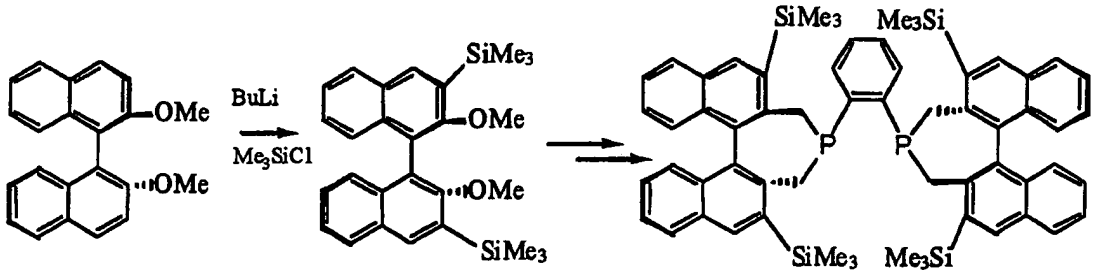
The highest enantioselectivity (>99%ee) has been achieved in the asymmetric hydrogenation of imines using Ir-f-binaphane complex as the catalyst.

The preparation of L1, L5, L17, L25, L36, L45, L51 and (*R,R*)-binaphane are illustrated below. Other members of L1 to L56 ligands can be prepared by similar procedures.

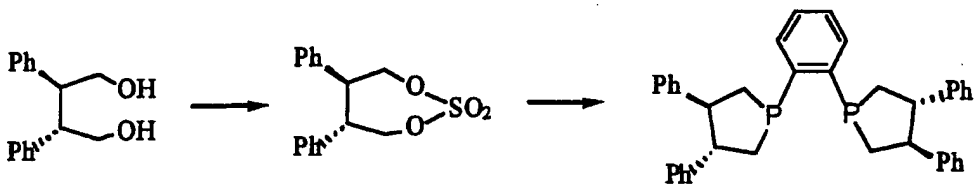


L1

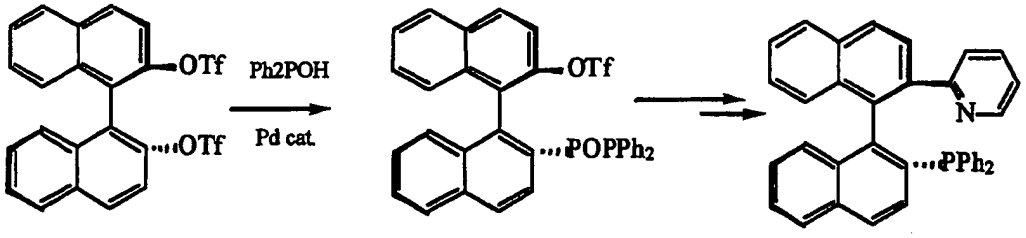
Binaphane



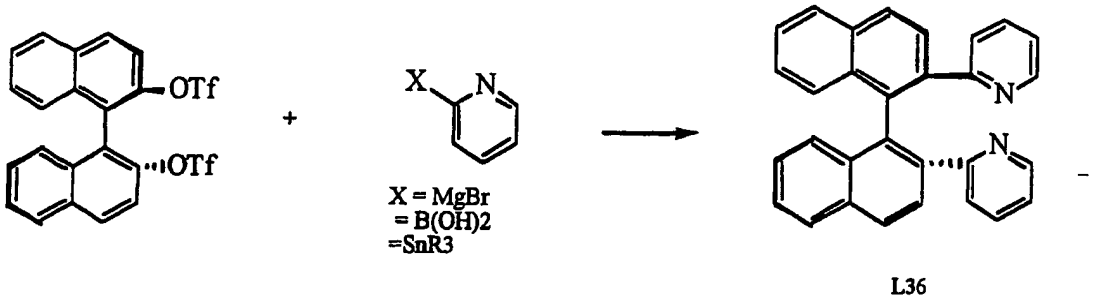
L5



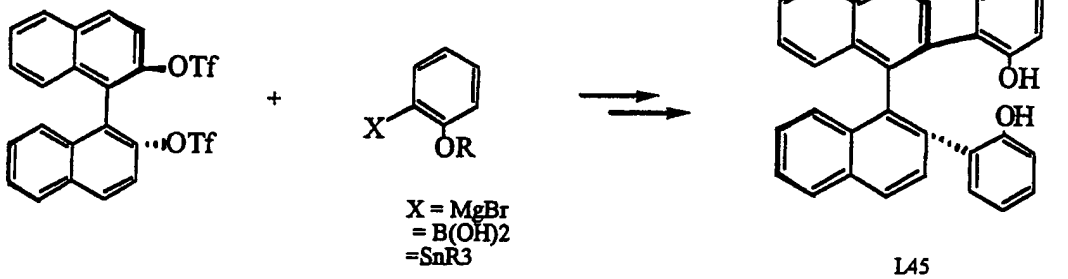
L17



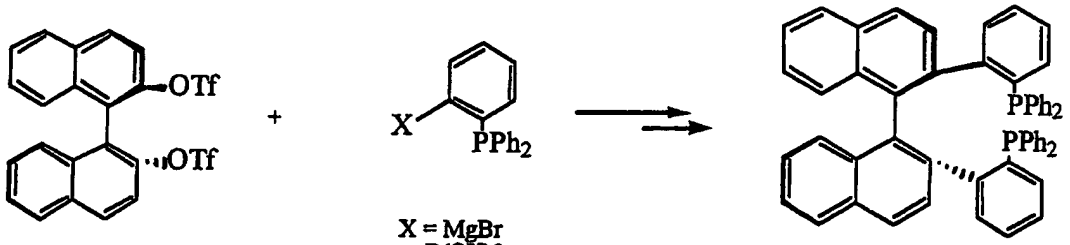
L25


OTf
OTf
X
N
X = MgBr
= B(OH)2
=SnR3
N
N

L36


OTf
OTf
X
OR
X = MgBr
= B(OH)2
=SnR3
OH
OH

L45

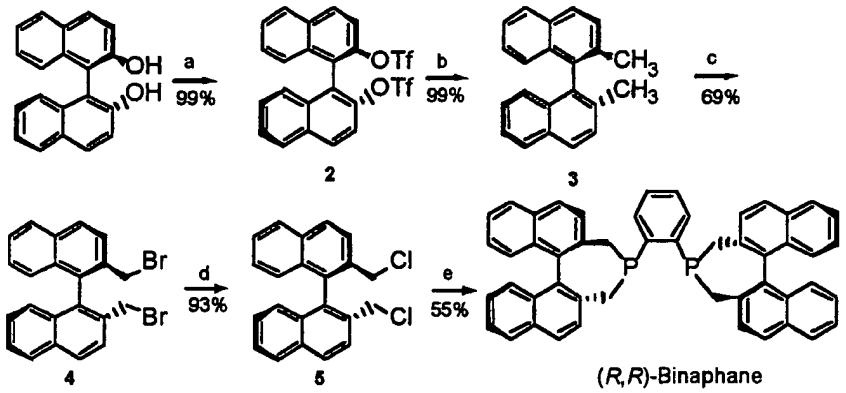

OTf
OTf
X
PPh2
X = MgBr
= B(OH)2
=SnR3
PPh2
PPh2

L51

The ligand according to the present invention can be racemic, i.e., racemic mixture of enantiomers, or a non-racemic mixture of enantiomers. Preferably, the ligand according to the present invention is one of the enantiomers. When the ligand is a non-racemic mixture of enantiomers, preferably it has an optical purity of at least 85% ee, more preferably, it has an optical purity of at least 95% ee.

According to the above reaction scheme, (*R,R*)-1,2-bis{(*R*)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]phosphenino}benzene, abbreviated as (*R,R*)-binaphane, has been prepared in high yield and high optical purity. This chiral chelating phosphine has a rigid 1,2-bis(phosphino)benzene backbone and has both binaphthyl chirality and a phospholane functionality.

The preparation procedure is illustrated below:



[a]Tf_2O, Py, CH_2Cl_2. [b]MeMgBr, $NiCl_2$(dppp), Et_2O. [c]NBS, Benzoyl peroxide, CCl_4. [d]LiCl, DMF. [e]1,2-Bisphosphinobenzene, NaH,

As illustrated schematically above, (*R,R*)-binaphane was prepared employing a practical synthesis route based on readily accessible starting materials. Enanatiomerically pure binaphthol can be easily obtained using a classic resolution procedure (Cai, D.; Hughes, D. L.; Verhoever, T. R.; Reider, P. J. *Tetrahedron Letter*, **1995**, 7991). (*R*)-2,2'-bistriflate-1,1'-binaphthyl (**2**) was made from (*R*)-binaphthol by treating with excess triflic anhydride and pyridine in CH_2Cl_2. Kumada coupling of bistriflate (**2**) with methyl magnesium bromide gave (*R*)-2,2'dimethyl-1,1'-binaphthyl (**3**) in high yield. (*R*)-2,2'-Dibromomethyl-1,1'-binaphthyl (**4**) was prepared by bromination of **3** with NBS. A simple anion exchange of (*R*)-2,2'-dibromomethyl-1,1'-binaphthyl (**4**) with LiCl afforded (*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (**5**) in high yield. A key element of our synthesis of chelating phospholane such as binaphane is utilization of a less reactive (*R*)-2,2'-dichloromethyl-1, 1'-binaphthyl (*5*) to avoid the intermolecular reaction with phosphine anions which existed when using a more reactive (*R*)-2,2'-dibromomethyl-1,1'-binaphthyl (**4**). Refluxing (*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (**5**) with 1,2-bis(phosphino)benzene and NaH in THF followed by recrystallization from ether gave (*R,R*)-binaphane in 55% yield. This efficient synthesis allows us to make binaphane in a large scale. Using this procedure, we have also made the corresponding monodentate chiral binaphthyl phospholane from phenylphosphine in >90% yield.

In a similar connectivity as in binaphane, new chiral five-membered ring chelating phospholanes with stereogenic centers in 3,4 positions can be effective. An important transformation in making the binaphthyl phospholane ligand is Kumada coupling of ArOTf with RMgBr (from **2** to **3**). Stille and Suzuki coupling may also work as well. Based on these coupling strategies, a series of new atropisomers of P,N ligands, N,N ligands, biphenols and chelating bisphophines can be derived.

Chiral f-binaphane (or a substituted derivative thereof) was prepared according to a process comprising contacting chiral 1,1'-di(chloromethyl)binaphthyl (or a substituted derivative thereof) and 1,1'-bisphosphinoferrocene (or a substituted derivative thereof) in the presence of a base and a solvent to produce f-binaphane (or the substituted derivative thereof). Preferably, the base is NaH and the solvent is tetrahydrofuran is (THF).

The present invention also includes a catalyst prepared by a process comprising contacting a transition metal salt, or a complex thereof, and a ligand selected from the group consisting of compounds represented by A through K.

As for the ligand, the catalyst according to the present invention can be racemic, such as, a racemic mixture of enantiomers, or it can be a non-racemic mixture of enantiomers. Preferably, the catalyst

according to the present invention is one of the enantiomers. When the ligand according to the present invention is a non-racemic mixture of enantiomers, preferably it has an optical purity of at least 85% ee, more preferably, it has an optical purity of at least 95% ee.

Suitable transition metals for the preparation of the catalyst include Pt, Pd, Rh, Ru, Ir, Cu, Ni, Mo, Ti, V, Re and Mn.

The catalyst can be prepared by contacting a transition metal salt or its complex and a ligand selected from A through K. The transition metal salt or complex can be $PtCl_2$; $Pd_2(DBA)_3$; $Pd(OAc)_2$; $PdCl_2(RCN)_2$; $[Pd(allyl)Cl]_2$; $[Rh(COD)Cl]_2$; $[Rh(COD)_2]X$; $Rh(acac)(CO)_2$; $Rh(ethylene)_2(acac)$; $Rh(CO)_2Cl_2$; $Ru(RCOO)_2(diphosphine)$; $Ru(methylallyl)_2(diphosphine)$; $Ru(aryl\ group)X_2(diphosphine)$; $RuCl_2(COD)$; $[Rh(COD)_2]X$; $RuX_2(diphosphine)$; $RuCl_2(=CHR)(PR'_3)_2$; $Ru(ArH)Cl_2$; $Ru(COD)(methylallyl)_2$; $[Ir(COD)_2Cl]_2$; $[Ir(COD)_2]X$; $Cu(OTf)$; $Cu(OTf)_2$; $Cu(Ar)X$; CuX; NiX_2; $Ni(COD)_2$; $MoO_2(acac)_2$; $Ti(OiPr)_4$; $VO(acac)_2$; $MeReO_3$; MnX_2 or $Mn(acac)_2$; wherein each R and R' can independently be alkyl or aryl; Ar is an aryl group; and X is a counteranion. The preferred counteranions include halogen, BF_4, ClO_4, SbF_6, CF_3SO_3 and a mixture thereof.

The catalyst may be prepared in situ or as an isolated compound. An example of the preferred catalyst

of the present invention is chiral Ir-f-binaphane catalyst.

In another aspect, the present invention includes a process for preparation of an asymmetric compounds using the catalysts described above. The process includes the step of contacting a substrate capable of forming an asymmetric product by an asymmetric reaction and a catalyst prepared by contacting a transition metal salt, or a complex thereof, and a ligand selected from ligands represented by A through K.

Suitable asymmetric reactions is include hydrogenation, hydride transfer, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition and epoxidation. Preferably, the asymmetric reaction is hydrogenation and the substrate to be hydrogenated is an ethylenically unsaturated compound, imine, ketone, enamine, enamide, and vinyl ester. Suitable catalysts for the hydrogenation of imines to produce a chiral amine include Ir complex of chiral f-binaphane and Rh complex of chiral binaphane.

To test synthetic utility of (*R,R*)-binaphane, asymmetric hydrogenation of enamides using a Rh-(*R,R*)-binaphane complex as the catalyst was conducted. The imine reduction may be carried out in the presence of additional catalysts, such as iodine or H^+.

Initially, several experiments were performed to screen optimal conditions for hydrogenation of *N*-acetyl-phenylethenamine. $Rh(COD)_2PF_6$ was found as a better catalyst precursor compared with a neutral Rh species $[Rh(COD)Cl]_2$. Increase of H_2 pressure results in decrease of enantioselectivity of the asymmetric hydrogenation. For example, 85%ee was obtained under 300 psi H_2 while 90%ee was achieved under 20 psi H_2. Variation of solvents causes dramatic changes in both enantioselectivity and reactivity. While hydrogenation was complete in CH_2Cl_2 with 90%ee, both reactivity and enantioselectivity were lower in methanol (14%ee and 86% conversion).

Several enamides were prepared according to literature procedures and were used as substrates for the asymmetric hydrogenation reaction. Table 1 lists results obtained under the optimal conditions for hydrogenation of *N*-acetyl-phenylethenamine (**6a**). Although very good enantioselectivity has been obtained for hydrogenation of α-arylenamides without substitituents in the β-position, the highlight of the Rh-binaphane catalyst is its ability to reduce β-substituted-α-arylenamides with excellent enantioselectivities. Several β-substituted-α-arylenamides with the mixture of (*E*)/(*Z*) isomers were reduced in high enantioselectivities (entries 7-13, 95%-99.6%ee). A small electronic effect was observed. These enantioselectivities with the Rh-(*R,R*)-binaphane catalyst is the highest reported to date. Since the product 7 can be easily converted to the corresponding

arylalkylamine through hydrolysis under acidic condition, hydrogenation with the Rh-binaphane complex provides a practical method for preparing a variety of chiral arylalkylamines.

EXAMPLES

General Procedures:

All reactions and manipulations were performed in a nitrogen-filled glove box or using standard Schlenk techniques. THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was distilled from CaH_2. Methanol was distilled from Mg under nitrogen. (*R,R*)-BDNPB was made a solution of 10mg/ml in toluene before use. Column chromatography was performed using EM silica gel 60 (230~400 mesh). ^{1}H, ^{13}C and ^{31}P NMR were recorded on Bruker WP-200, AM-300, and AMX-360 spectrometers. Chemical shifts were reported in ppm down field from tetramethylsilane with the solvent resonance as the internal standard. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-EI and HR-EI. GC analysis was carried on Helwett-Packard 6890 gas chromatography using chiral capillary columns. HPLC analysis was carried on Waters™ 600 chromatography. Imines were prepared according to a reported procedure.

Synthesis of 1,2-Bis{(*R*)-4,5-dihydro-3H-dinaphtho[1,2-c;2',1'-e]phosphepino}benzene:

(*R*)-2,2'-bistriflate-1,1'-binaphthyl (2):

To a solution of (*R*)-BINOL (40.3 g, 140.7 mmol) in 900 mL of CH_2Cl_2 was added pyridine (40 mL) and followed by dropwise addition of triflic anhydride (50.5 mL, 300 mmol) at 0°C. The mixture was stirred at room temperature for 6h. After removal of the solvent, the residue was diluted with EtOAc (500 mL) and then washed with 5% aqueous HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and passed through a silica gel plug (eluted with CH_2Cl_2) to give the (*R*)-bistriflate (2) (77 g, 99%).

(*R*)-2,2'-dimethyl-1,1'-binaphthyl (3):

To a solution of (*R*)-bistriflate (2) (77 g, 140 mmol) and $NiCl_2$•dppp (3.8 g, 7 mmol) in ether (1000 mL) was added dropwise the methyl magnusium bromide (3.0 M, 280 mL) at 0°C. The reaction mixture was heated to refluxing for 24h. The reaction was quenched by addition of water (200 mL) slowly at 0°C and then diluted with 5% aqueous HCl (200 mL). The aqueous layer was extracted with ether (3 x 100 mL). The combined organic layer was washed with $NaHCO_3$(100 mL), dried over anhydrous sodium sulfate and concentrated to afford **3** as light yellow color solid (39.2 g, 99%).

(*R*)-2,2'-dibromomethyl-1,1'-binaphthyl (4):

A mixture of (R)-2,2'-dimethyl-1,1'-binaphthyl (**3**) (39.2 g, 138.8 mmol), *N*-bromosuccinimide (52.4 g, 291.5 mmol) and benzoylperoxide (0.5 g) in tetrachlorocarbon (900 mL) was heated at refluxing and irradiated under a sunlight for three days. The mixture was cooled to room temperature and filtered. The filtrate was concentrated and passed through a silica gel plug. After removal of the solvent, the residue was recrystalized from CH_2Cl_2/hexanes to afford 2,2'-dibromomethyl-1,1'-dinaphthyl (**4**) (41.1 g, 67.3 %).

(*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (5):

(*R*)-2,2'-Dibromomethyl-1,1'-binaphthyl (**4**, 40 g, 90.8 mmol) and LiCl (30 g, 707 mmol) in DMF (800 mL) was mixed together and stirred at room temperature for 6h. To this mixture was added carefully 5% aqueous HCl (300 mL) (exothermomic reaction occurred). The mixture was then extracted with ether (4 x 400 mL). The organic layer was dried over sodium sulfate, concentrated and recrystallized from CH_2Cl_2/hexane to gave **5** as white solid (30 g, 93%).

(*R,R*)-1,2-bis{(*R*)-4,5-dihydro-3H-dinaphtho[1,2-c;2',1'-e]phosphepino}benzene:

To a solution of (*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (**5**, 0.57 g, 1.62 mmol) and NaH (0.2 g, 8.3 mmol) in THF (20ml) was added 1,2-bis(phosphino)benzene

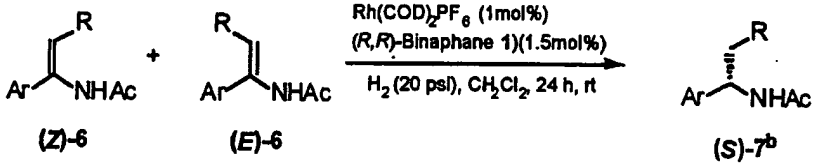
(109 µl, 0.812 mmol) at -78°C under nitrogen. The mixture was kept stirring at room temperature for 24h and was heated at refluxing for 24 h. After the reaction was completed (monitored by ^{31}P NMR), the solvent was removed via vacuum and the residue was washed with ether (3 x 15 mL). The organic phase was filtered through a silica gel plug to give the fairly pure product. Further purification by recrystallization from ether afforded binaphane (0.31 g, 55%). ^{1}H NMR ($CDCl_3$) 360MHz 7.83-7.8 (4H,m,Ar-H), 7.59-7.56 (2H,m,Ar-H), 7.33-7.15 (16H,m,Ar-H), 7.0-6.9 (2H,m,Ar-H), 6.8-6.7 (2H,m,Ar-H), 6.66-6.63 (2H,d,*J* = 8.3Hz,Ar-H), 2.97-2.74 (8H, m, $ArCH_2$); ^{31}P NMR($CDCl_3$) -5.63 ppm.

General Procedure for Catalytic Asymmetric Hydrogenation of Enamides:

In a glove box, the Rh-phosphine complex was made *in situ* by mixing $Rh(COD)_2PF_6$ (3.7 mg, 0.008 mmol) and binaphane (0.8 mL of 10mg/mL ligand in toluene, 0.012 mmol) in 19.2 mL of CH_2Cl_2. The mixture was stirred for 30 min. Then 2.5 mL of this solution was transferred to a 10 mL vial with an enamide substrate (0.1 mmol). Hydrogenation was performed at room temperature under 20 psi of hydrogen pressure for 24 h. The hydrogen was released carefully and the reaction mixture was passed through a silica gel plug eluted with EtOAc. The enantiomeric excess was measured by GC or HPLC using a chiral GC or HPLC column without further purification. The absolute configuration of products was determined by

comparing the sign of optical rotation with the reported data (Table 1).

Table 1. Highly Enantioselective Hydrogenation of Enamides Catalyzed by Rh-(*R,R*)-Binapthane Complex [a]



(Z)-6 (E)-6 (S)-7[b]

Entry	Substrate[c]	Ar	R	ee %[d]
1	6a	C_6H_5	H	90.0
2	6b	3-Me-C_6H_4	H	89.0
3	6c	4-CF_3-C_6H_4	H	82.0
4	6d	4-Ph-C_6H_4	H	75.7
5	6e	4-Cy-C_6H_4	H	90.0
6	6f	2-Np	H	89.5
7	6g	C_6H_5	CH_3	99.1
8	6h	4-MeO-C_6H_4	CH_3	99.6
9	6i	4-CF_3-C_6H_4	CH_3	97.0
10	6j	C_6H_5	CH_2CH_3	97.0
11	6k	C_6H_5	CH_2Ph	95.0
12	6l	C_6H_5	$CH(CH_3)_2$	97.6
13	6m	2-Np	CH_3	98.3

[a] The reaction was carried out at rt under an initial hydrogen pressure of 20 psi for 24 h. The catalyst w made *in situ* by stirring a soluton of $Rh(COD)_2PF_6$ and (*R, R*)-Binaphane in CH_2Cl_2. [Substrate(0.04M)]: [Rh] : (*R, R*)-Binaphane = 100 : 1 : 1.5. The reaction went in quantitative yield. [b] The configuration of product was determined by comparison of optical rotation with reported data. [c] Enamides 6 were made according to the literature methods. [d] Enantiomeric excesses were deterimined by chiral GC with a supelco chiral select 1000 column or by Chiral HPLC with a Regis (*S,S*)-Whelk-o1 column.

Highly enantioselective reduction of C-N double bond has drawn much attention in last few decades. Catalytic asymmetric hydrogenation of acyclic imines has remained among the toughest problems in synthetic chemistry despite several systems being effective in asymmetric hydrogenation of cyclic imines.

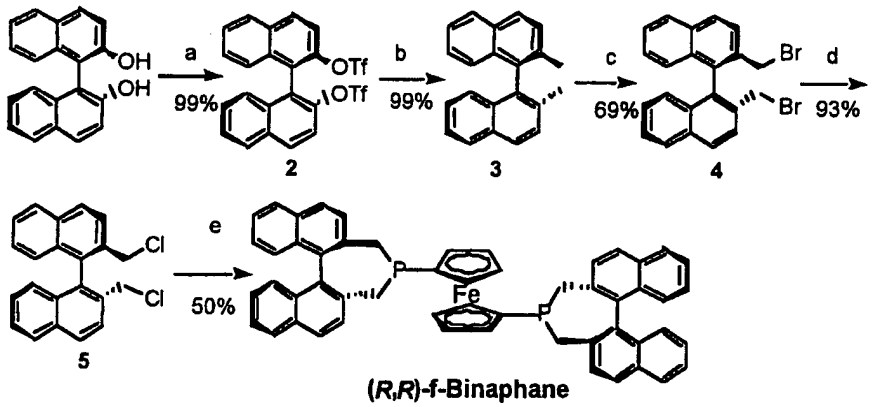
Recently Pfaltz et al. has reported that up to 89%ee can be achieved in enantioselective hydrogenation of N-phenyl imine of acetophenone with an Ir-P-N ligand complex as the catalyst. Enantioselectivities exceeding 90%ee in asymmetric hydrogenation of acyclic imines have rarely been reported in the literature.

According to the present invention, a high enantioselectivity (>99%ee) has been achieved in the synthesis of new chiral ligand (f-binaphane) and in the asymmetric hydrogenation using Ir-f-binaphane complex as the catalyst.

Synthesis of Chiral Phosphines (f-Binaphane):

This ligand was made via a route similar to that used to make binaphane. The 1,1'-diphosphinoferrocene was employed as the backbone to afford the new ligand more electron donating property that might be beneficial in transition metal catalyzed asymmetric reactions.

Synthesis of Chiral Phosphine f-Binaphane



[a]Tf_2O, Py, CH_2Cl_2. [b]MeMgBr, $NiCl_2$(dppp), Et_2O. [c]NBS, Benzoyl peroxide, CCl_4. [d]LiCl, DMF. [e]1,1'-Diphosphinoferrecene, NaH, THF.

5

(*R,R*)-1,1'-bis{(*R*)-4,5-dihydro-3H-dinaphtho[1,2-c:2',1'-e]phosphepino}ferrocene:

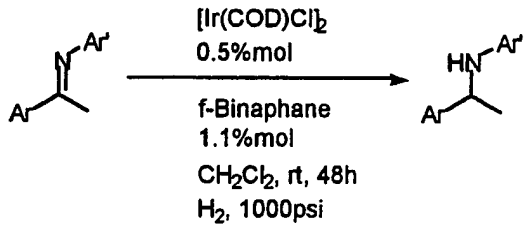
To a solution of (*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (5, 3.71 g, 10.56 mmol, prepared from (*R*)-BINOL *via* (*R*)-2,2'-bistriflate-1,1'-binaphthyl (2)[1], (*R*)-2,2'-dimethyl-1,1'-binaphthyl (3)[2], (*R*)-2,2'-dibromomethyl-1,1'-binaphthyl (4)[3], (*R*)-2,2'-dichloromethyl-1,1'-binaphthyl (5)[4] as previously described above) and NaH (2.0 g, 83.0 mmol) in THF (125ml) was added 1,1'-di(phosphino)ferrocene (1.32g, 5.28 mmol) at -78°C under nitrogen. The mixture was kept stirring at room temperature for 24 h and was heated at refluxing for 24 h. After the reaction was completed (monitored by ^{31}P NMR), the solvent was

removed via vacuum and the residue was washed with CH_2Cl_2 (3 x 25 mL). The organic phase was filtered through a silica gel plug to give the fairly pure product. Further purification by recrystallization from Hexanes afforded (*R,R*)-1,1'-bis{(*R*)-4,5-dihydro-3H-dinaphtho[1,2-c:2',1'-e]phosphepino}ferrocene (2.15 g, 50%). ^1H NMR ($CDCl_3$) 360MHz δ 7.81-7.76 (8H, m, Ar-H), 7.57-7.54 (4H, m, Ar-H), 7.31-7.13 (10H, m, Ar-H), 7.00-6.90 (2H, m, Ar-H), 6.80-6.70 (2H, m, Ar-H), 6.64-6.62 (2H,d, *J* = 8.34 Hz, Ar-H), 2.97-2.74 (8H, m, $ArCH_2$); ^{13}C NMR ($CDCl_3$) δ 141.70, 134.71, 134.21, 133.40, 133.27, 132.73, 132.54, 132.34, 131.20, 128.83, 128.69, 128.62, 128.08, 127.80, 127.13, 127.10, 126.32, 125.46, 125.26, 32.50, 29.83; ^{31}P NMR($CDCl_3$) δ -6.87. MS m/z: 698 (M^+). (References: (1) Uozumi, Y.; Tanahashi, A.; Lee, S-Y.; Hayashi, T. *J. Org. Chem.* **1993**, 58, 1945; (2) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, 57, 4066; (3) Maigrot, N.; Mazaleyrat, J-P. *Synthesis*, **1985**, 317; and (4) Chong, J. M.; MacDonald, G. K.; Park, S. B.; Wilkinson, S. H. *J. Org. Chem.* **1993**, 58, 1266).

Enantioselective Hydrogenation of Imines:

The N-phenyl imine of acetophenone was used to screen the reacion condition. Finally, the optimized condition was set as described below.

Enantioselective Hydrogenation of Acyclic Imines Catalyzed by Ir-f-Binaphane



Conversion	100%	100%	80.3%	77.2%
ee	84.5%	>99%	98.8%	97.8%

Other substrates were tried and we found that the bigger N-aryl group plays a very important role for high enantioselectivities. Changing the aryl group of aryl-alkyl ketone has no obvious effect on enantioselectivity.

General Procedure for Catalytic Asymmetric Hydrogenation of Imines:

In a glove box, the Ir-phosphine complex was made *in situ* by mixing $[Ir(COD)Cl]_2$ (6.7mg, 0.01 mmol) and the phosphine complex (0.022 mmol) in 20 mL of CH_2Cl_2 and stirring for 30 min. Then 5 mL of the solution was transferred to a 10mL vial with an imine substrate (0.5 mmol). The hydrogenation was performed at rt under 1000

psi of hydrogen pressure for 48 h. The hydrogen was released carefully and the reaction mixture was passed through a silica gel plug eluted with EtOAc. The enantiomeric excess was measured by using GC with a chiral GC column without further purification.

In addition to the chiral ligand binaphane, which has been prepared from chiral BINOL and has shown excellent performance in Rh-catalyzed asymmetric hydrogenation of enamides, the present invention further includes a new chiral chelating phosphine, f-binaphane, which similarly bears binaphthyl moieties but is connected by a 1,1'-bisphosphinoferrocene backbone.

The new ligand, f-binaphane, was synthesized by a route similar to the preparation binaphane. Chiral binol was transformed into bistriflates **2**, followed by dimethylation through Kumada coupling, bromination with NBS and anion exchanging with LiCl, afforded 1,1'-di(chloromethyl)binaphthyl **5**. Refluxing dicholoride **5** with 1,1'-bisphosphinoferrocene in the presence of NaH in THF, followed by recrystallization from CH_2Cl_2/Hexanes, gave the pure f-binaphane product as a yellow solid.

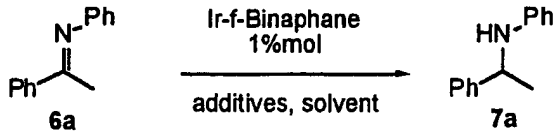
In addition to the simple synthetic route, the stability of the f-binaphane ligand in the air as well as in solvent (at least for two days) makes the new ligand more attractive.

One of the important features of f-binaphane is its electron-rich property due to the two methylene groups and the ferrocene backbone binding to the phosphorus atom. This feature may be responsible for higher asymmetric induction for hydrogenation of unsaturated compounds. Another important feature is the flexibility of the ferrocene backbone that enables the f-binaphane ligand to chelate different transition metals as easily as BINAP does.

Furthermore, the coordination of the transition metal with chiral ligand will fix the configuration of the complex and provide a prominent chiral environment in which two binaphthyl groups occupy exactly two opposite quadrants, leaving the other two quadrants vacant. As a result, the ferrocene backbone makes the chiral pocket even broader and deeper and thus accessible to many bulky substrates.

The new ligand was applied to the so far unsolved imine reduction problem. In contrast to many catalytic enantioselective hydrogenation of olefins and ketones, only very limited success has been achieved by others in asymmetric hydrogenation of imines. The first attempt of f-Bianphane in hydrogenation of N-(1-phenylethylidene)aniline produced 84%ee at room temperature with 1% Ir-catalyst loading. The optimal condition was screened using the same substrate as the model substrate. The results are summarized in Table 2 below.

Table 2. Enantioselective Hydrogenation of N-(1-Phenylethylidene)aniline Catalyzed by Ir-f-Binaphane Complex[a]



entry	additive	solvent	T/°C	P_{H_2}/psi	t/h	conversion%	ee%[b]
1	—	CH_2Cl_2	rt	1000	40	100	84.0
2	—	THF	rt	1000	40	97.2	83.3
3	—	Toluene	rt	1000	40	75.8	23.4
4	—	MeOH	rt	1000	40	71.2	64.0
5	—	CH_2Cl_2	rt	400	48	97.8	84.0
6	—	CH_2Cl_2	-5	1000	64	94.5	84.0
7	Phthalimide 4%	CH_2Cl_2	rt	1000	24	100	82.7
8	$^nBu_4NI$ 4%	CH_2Cl_2	rt	1000	24	100	72.9
9	$PhCH_2NH_2$ 4%	CH_2Cl_2	rt	1000	24	8.8	62.0
10	AcOH 35eq	CH_2Cl_2	rt	1000	24	48	71.8

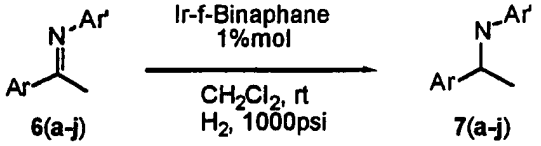
[a] The reaction was carried out in autoclave by mixing the substrate with catalyst in solvent and pressurized with hydrogen. The catalyst was made in situ by stirring a solution of $[Ir(COD)Cl]_2$ and (R,R) f-Binaphane in solvent. [Substrate (0.1M)] : [Ir] : (R,R) f-Binaphane =100:1:1.1. [b] Enantiomeric excess was deterimined by chiral GC with a Supelco chiral select 1000 column. Absolute configurations was not deterimined.

Neutral precursor $[Ir(COD)Cl]_2$ has better performance than cationic $Ir(COD)_2PF_6$. The weakly coordinating solvent CH_2Cl_2 is preferred over other solvent such as THF, toluene or MeOH (entries 1-4). Decreasing the hydrogen pressure has no obvious improvement on enantioselectivity but drops the reactivity (entry 5). The temperature effect is negligible (entry 6). The additive effect that shows a great improvement on enantioselectivity in many systems was not found in this case (entries 7-10). However, phthalimide and tetrabutylammonium iodide did accelerate the reaction to a small extent (entries 7-8).

When 2,6-dimethylphenyl group was employed to replace N-phenyl group, surprisingly >99% enantioselectivity was achieved. To our knowledge, this is the highest enantioselectivity achieved so far for asymmetric hydrogenation of acyclic imines.

These results are summarized in Table 3.

Table 3. Enantioselective Hydrogenation of Acyclic Imines Catalyzed by Ir-f-Binaphane Complex



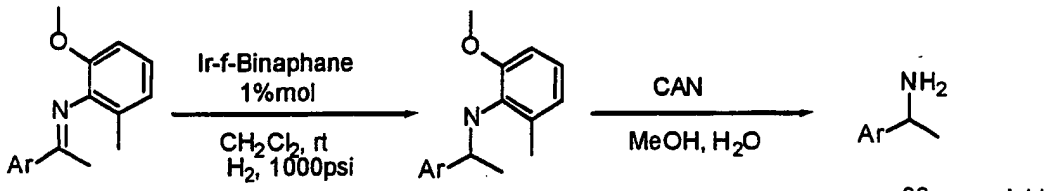
entry	substrate	Ar	Ar'	t/h	conversion%	ee%[b]
1	6a	Ph	Ph	40	100	84.0
2	6b	Ph	2,6-dimethyl-C_6H_3	44	76.8	>99
3	6c	4-MeO-C_6H_4	2,6-dimethyl-C_6H_3	44	77.2	97.8
4	6d	4-CF_3-C_6H_4	2,6-dimethyl-C_6H_3	44	80.3	98.8
5	6e	N-(2,3,4-trihydro-1-naphthylidene) 2,6-dimethylaniline		44	23.8	96.8
6	6f	t-Bu	2,6-dimethyl-C_6H_3	44	14.9	8.3
7	6g	^{i}Pr	2,6-dimethyl-C_6H_3	44	28.8	22.6
8	6h	Cy	2,6-dimethyl-C_6H_3	44	24.2	31.4
9	6i	Ph	4-MeO-C_6H_4	12	100	76.6
10	6j	Ph	2-MeO-C_6H_4	14	100	81.4

[a] The reaction was carried out at room temperature under an initial hydrogen pressure of 1000psi. The catalyst was made in situ by stirring a solution of $[Ir(COD)Cl]_2$ and (R,R) f-Binaphane in CH_2Cl_2. [Substrate (0.1M)] : [Ir] : (R,R) f-Binaphane =100:1:1.1.
[b] Enantiomeric excesses were deterimined by chiral GC with a Supelco chiral select 1000 column. Absolute configurations were not deterimined.

Changing the electronic property of Ar group has little effect on both reactivity and enantioselectivity (entries 3-4), but replacing the Ar with alkyl group cause a substantial drop of enantioselectivity and reactivity(entries 6-8). The high enantioselectivity (96.8%ee) and low reactivity (23.8% yield) was achieved for the ketamine derived from α-tetralone(entry 5). Replacement of N-Ar' group with methoxyl substituted

phenyl group has great improvement in reactivity without any increment of enantioselectivity (entries 9-10). This is understandable that the electron donating methoxyl group can destablize the conjugate system and activated the C=N bond. Base on above facts, the highest enantioselectivity of substrate N-2,6-dimethylphenyl ketaimine may be attributable to the steric effect rather than the electronic effect of the dimethyl group.

Two substrates (**6k** and **6l**) have been tried under the optimal hydrogenation condition with complete conversions. The hydrogenation products were subjected to deprotection with CAN in MeOH and water at 0°C. After workup, the chiral amines were purified by chromatography on silica gel. The enantioselectivities (98.1%ee and 95.7%ee for **8k** and **8l** respectively) are comparable to their uncleavable analogues. The highly enantioselective hydrogenation of acyclic imines is illustrated below.



6(k-l)

6k Ar=Ph
6l Ar=1-Np

7(k-l)

	ee	yield
8k	98.1%(S)	72%
8l	95.7%(S)	75%

Thus, the Ir-f-binaphane complex of the present invention, having a chiral ligand with binaphthyl motif connected by a ferrocene backbone, produces the highest enantioselectivity yet achieved for asymmetric hydrogenation of acyclic imines.

The significance of the new methodology is that it provides a practical method for the synthesis of chiral primary amines.

General Procedure for the synthesis of imines 6(a-l):

The ketone (1eq) and the appropriate amine (1eq) were dissolved in dry toluene (40ml) in a flask under nitrogen. The catalytic amount of p-toluenesulfonic acid was added. The flask was equipped with a reflux condenser and a Dean-Stark trap and the mix was heated to reflux for 5hrs. The reaction was quenched by adding saturated $NaHCO_3$ solution and extracted with ether (3x100ml). The organic layer was combined, washed with brines, dried (Na_2SO_4) and either distilled *in vacuo* or chromatographed on basic Al_2O_3.

N-(1-Phenylethylidene)aniline (6a): Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F.-M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, 887.

N-(1-Phenylethylidene)2,6-xylxlamine(6b): Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F.-M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, 887 and Okamoto, H.;

Kato, S.; Ogasawara, M.; Konnai, M.; Takematsu, T. *Agric. Biol. Chem.; EN*, 55, 11, **1991**, 2733.

N-(1-p-Methoxyphenylidene)2,6-xylxlamine (6c): Okamoto, H.; Kato, S.; Ogasawara, M.; Konnai, M.; Takematsu, T. *Agric. Biol. Chem.; EN*, 55, 11, **1991**, 2733.

N-(1-p-Trifluromethylphenylidene)2,6-xylxlamine (6d): ^{1}H NMR ($CDCl_3$, 300MHz), δ8.06-8.04(2H, d, J=6.73Hz, Ar-H), 7.64-7.62(2H, d, J=6.91Hz, Ar-H), 6.99-6.96(2H, d, J=6.30Hz, Ar-H), 6.87-6.83(1H, t, Ar-H), 2.00(3H, s, CH_3), 1.93(6H, s, $ArCH_3$) ^{13}C NMR($CDCl_3$, 300MHz), δ164.75, 148.86, 142.49, 133.16, 132.80, 132.44, 132.08, 128.96, 128.38, 127.88, 125.93, 125.87, 125.83, 125.79, 125.75, 123.61, 122.94, 119.93, 18.30, 17.91ppm.

N-(2,3,4-Trihydro-1-naphthylidene)2,6-xylxlamine (6e): ^{1}H NMR($CDCl_3$, 360MHz) δ8.86-8.84(1H, d, J=7.69Hz, Ar-H), 7.76-7.66(2H, m, Ar-H), 7.58-7.56(1H, d, J=7.39Hz, Ar-H), 7.43-7.41(2H, d, J=7.45Hz, Ar-H), 7.30-7.26(1H, t, Ar-H), 3.28-3.24(2H, t, CH_2), 2.64-2.60(2H, t, CH_2), 2.41(6H, s, CH_3), 2.29-2.22(2H, m, CH_2). ^{13}C NMR ($CDCL_3$, 360MHz) δ165.52, 149.61, 141.71, 134.10, 131.17, 129.32, 128.36, 128.06, 126.95, 126.18, 123.12, 30.57, 30.51, 23.36, 18.59ppm.

N-(1-Tetrabutylethylidene)2,6-xylxlamine (6f): ^{1}H NMR ($CDCl_3$, 360MHz), δ7.22-7.20(2H, d, J=7.56Hz, Ar-H), 7.08-7.04(1H, t, Ar-H), 2.19(3H, s, CH_3), 1.84(3H, s, CH_3), 1.50(6H, s, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ177.29,

149.33, 128.63, 128.28, 127.97, 125.70, 122.93, 122.65, 122.31, 40.98, 28.46, 18.06, 15.69ppm.

N-(1-Isopropylethylidene)2,6-xylxlamine (6g): ^{1}NMR ($CDCl_3$, 360MHz) δ7.00-6.98(2H, d, J=7.52Hz, Ar-H), 6.87-6.83(1H, t, Ar-H), 2.73-2.65(1H, m, CH), 1.99(6H, s, $ArCH_3$), 1.59(3H, s, CH_3), 1.25-1.21(6H, d, J=13.60Hz, CH_3, major isomer (E)), 0.99-0.97(6H, d, J=6.84Hz, CH_3, minor isomer (Z)) [(E)/(Z)=14:1], ^{13}C NMR ($CDCl_3$, 360MHz) δ175.91, 149.10, 128.23, 126.04, 122.80, 39.22, 20.41, 18.08, 17.93ppm.

N-(1-Cyclohexylethylidene)2,6-xylxlamine (6h): ^{1}HNMR ($CDCl_3$, 360MHz) δ6.89-6.87(2H, d, J=7.46Hz, Ar-H), 6.76-6.72(1H, t, Ar-H), 2.27-2.25(1H, m, CH), 1.88(6H, s, $ArCH_3$), 1.92-1.50(5H, m, CH_2), 1.49(3H, s, CH_3), 1.49-1.22(5H, m, CH_2). ^{13}C NMR ($CDCl_3$, 360MHz) δ175.37, 149.21, 127.88, 125.98, 122.73, 49.41, 30.93, 26.64, 18.60, 18.15ppm.

N-(1-Phenylidene)4'-methoxyaniline (6i): Milart, P.; Sepiol, J. *Z. Naturforsch. B. Anorg. Chem. Org. Chem. EN.* 41, 3, **1986**, 371.

N-(1-Phenylidene)2'-methoxyaniline (6j): Okamoto, H.; Kato, S.; Ogasawara, M.; Konnai, M.; Takematsu, T. *Agric. Biol. Chem.; EN*, 55, 11, 1991, 2733.

N-(1-Phenylidene)2'-methoxy-6'-methylaniline (6k): ^{1}H NMR ($CDCl_3$, 360MHz) δ8.39-8.36(2H, m, Ar-H), 7.76-

7.73(3H, m Ar-H), 7.31-7.28(1H, t, Ar-H), 7.18-7.16(1H, d, J=7.57Hz, Ar-H), 7.10-7.08(1H, d, J=8.09Hz), 4.03(3H, s, OCH_3), 2.42(3H, s, CH_3), 2.41(3H, s, CH_3). ^{13}C NMR ($CDCL_3$, 360MHz) δ167.18, 148.68, 139.77, 139.45, 130.81, 129.04, 128.91, 128.76, 128.52, 128.29, 127.76, 126.63, 126.30, 124.14, 123.83, 123.02, 109.46, 56.10, 18.29ppm.

N-(1-(1-Naphthyl)ethylidene)2'-methoxy-6'-methylaniline (61): ^1H NMR ($CDCl_3$, 360MHz) δ8.65-8.62(1H, d, J=8.49Hz, Ar-H), 7.94-7.92(2H, d, J=8.04Hz, Ar-H), 7.69-7.67(1H, d, J=8.13Hz, Ar-H), 7.62-7.54(3H, m, Ar-H), 7.08-7.06(1H, t, Ar-H), 6.96-6.70(2H, m, Ar-H), 3.93(3H, s, OCH_3), 2.28(3H, s, CH_3), 2.24(3H, s, CH_3). ^{13}C NMR($CDCl_3$, 360MHz) δ171.60, 148.38, 140.45, 139.34, 134.39, 130.93, 129.55, 128.91, 128.75, 128.63, 127.01, 126.40, 125.46, 125.16, 124.01, 123.02, 108.49, 56.30, 23.02, 18.70, 18.40ppm.

General Procedure for Catalytic Asymmetric Hydrogenation of Imines:

The Ir-f-binaphane complex was made *in situ* by mixing $[Ir(COD)Cl]_2$ (6.7 mg, 0.01 mmol) and f-binaphane (17.7mg, 0.022 mmol) in 20mL of CH_2Cl_2. The mixture was stirred for 30 min. Then 5 mL of this solution was transferred to a 10mL vial with an imine substrate (0.5 mmol). The hydrogenation was performed at rt under 1000 psi of hydrogen. After the reaction, the hydrogen was released carefully and the reaction mixture was passed through a silica gel plug eluted with CH_2Cl_2. The enantiomeric excess was measured by using GC with a

chiral column without further purification. The absolute configuration of products was determined by comparing the retention time with the standard chiral compounds.

N-Phenyl-1-phenylethylamine (7a): Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F.-M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, 887.

N-(2',6'-Dimethylphenyl)-1-phenylethylamine (7b): ^{1}H NMR ($CDCl_3$, 360MHz) δ7.19-7.10(5H, m, Ar-H), 6.85-6.83(2H, d, J=7.41Hz, Ar-H), 6.70-6.66(1H, t, Ar-H), 4.24-4.19(1H, q, CH), 3.09(1H, b, NH), 2.07(6H, s, $ArCH_3$), 1.42-1.39(3H, d, J=6.76Hz, CH_3). ^{13}C NMR($CDCl_3$, 360MHz) δ145.75, 145.39, 129.93, 129.33, 128.91, 127.48, 126.61, 122.11, 57.27, 23.13, 19.40ppm.

N-(2',6'-Dimethylpheny)-1-p-Methoxyphenylethylamine (7c): ^{1}H NMR ($CDCl_3$, 360MHz) δ7.35-7.33(2H, d, J=6.93Hz, Ar-H), 7.09-7.07(2H, d, J=7.51Hz, Ar-H), 6.98-6.90(3H, m, Ar-H), 4.44-4.39(1H, q, CH), 3.91(3H, s, OCH_3), 3.30(1H, b, NH), 2.31(6H, s, $ArCH_3$), 1.63-1.61(3H, d, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz), δ159.00, 145.31, 137.87, 129.91, 129.23, 127.63, 122.02, 114.06, 56.50, 55.83, 22.98, 19.35ppm.

N-(2',6'-Dimethylphenyl)-1-p-Trifluromethylphenyl ethylamine (7d): ^{1}NMR ($CDCl_3$, 300MHz), δ7.49-7.46(2H, d, J=8.24Hz, Ar-H), 7.35-7.32(2H, d, J=8.21Hz, Ar-H), 6.89-6.87(2H, d, J=7.47Hz, Ar-H), 6.75-6.70(1H, t, Ar-H). 4.32-4.25(1H, q, CH), 3.11(1H, b, NH), 2.08(6H, s,

$ArCH_3$), 1.47-1.44(3H, d, J=6.74Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz), δ144.90, 129.74, 129.37, 126.87, 126.40, 125.82, 122.80, 122.35, 56.98, 23.26, 19.30ppm.

N-(2',6'-Dimethylphenyl)-2,3,4-trihydro-1-naphthylamine (7e): The ^{1}NMR spectrum was consistent with **7e**.

N-(2',6'-Dimethylphenyl)-1-Tetrabutylethylamine (7f): ^{1}NMR ($CDCl_3$, 360MHz) δ6.88-6.85(2H, d, J=7.44Hz, Ar-H), 6.69-6.65(1H, t, Ar-H), 3.08-3.02(1H, q, CH), 2.82(1H, b, NH), 2.16(6H, s, $ArCH_3$), 0.96(9H, s, CH_3), 0.79-0.77(3H, d, J=6.49Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ145.78, 129.46, 129.29, 121.31, 60.29, 35.33, 27.00, 19.73, 15.75ppm.

N-(2',6'-Dimethylphenyl)-1-Isopropylethylamine (7g): ^{1}H NMR ($CDCl_3$, 360MHz) δ6.90-6.88(2H, d, J=7.46Hz, Ar-H), 6.71-6.67(1H, t, ArH), 3.14-3.07(1H, m, CH), 2.90(1H, b, NH), 2.18(6H, s, $ArCH_3$), 2.14-1.66(1H, m, CH), 0.94-0.86(9H, m, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ145.57, 129.34, 129.07, 121.30, 57.49, 33.87, 19.91, 19.58, 17.99, 17.22ppm.

N-(2',6'-Dimethylphenyl)-1-Cyclohexylethylamine (7h): ^{1}H NMR ($CDCl_3$, 360MHz) δ6.90-6.88(2H, d, J=7.42Hz, Ar-H), 6.72-6.68(1H, t, Ar-H), 3.08-3.03(1H, m, CH), 2.91(1H, b, NH), 2.18(6H, s, $ArCH_3$), 1.91-1.55(5H, m, CH/CH_2), 1.17-1.08(6H, m, CH_2), 0.89-0.87(3H, d, J=6.51Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ129.24, 128.22,

121.36, 57.29, 44.52, 30.43, 28.80, 27.12, 27.01, 26.90, 19.57ppm.

N-(p-Methoxyphenyl)-1-phenylethylamine (7I): ^{1}H NMR ($CDCl_3$, 360MHz) δ7.27-7.20(4H, m, Ar-H), 7.13-7.10(1H, t, Ar-H), 6.60-6.58(2H, d, J=6.69Hz, Ar-H), 6.37-6.35(2H, d, J=6.70Hz, Ar-H), 4.33-4.28(1H, m, CH), 3.58(1H, b, NH), 3.57(6H, s, $ArCH_3$), 1.39-1.37(3H, d, J=6.70Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ152.39, 145.95, 142.00, 129.09, 127.30, 126.38, 115.23, 115.07, 56.17, 54.74, 25.57ppm.

N-(o-Methoxyphenyl)-1-phenylethylamine (7j): ^{1}H NMR ($CDCl_3$, 360MHz) 7.28-7.26(2H, d, J=8.60Hz, Ar-H), 7.26-7.18(2H, m, Ar-H), 7.10-7.04(1H, t, Ar-H), 6.67-6.58(2H, m, Ar-H), 6.51-6.48(1H, t, Ar-H), 6.26-6.24(1H, d, J=7.75Hz, Ar-H), 4.57(1H, b, NH), 4.40-4.35(1H, m, CH), 3.77(3H, s, OCH_3), 1.46-1.44(3H, d, J=6.76Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ147.05, 145.88, 137.62, 129.07, 127.26, 126.32, 121.63, 116.83, 111.56, 109.74, 55.88, 53.81, 25.62ppm.

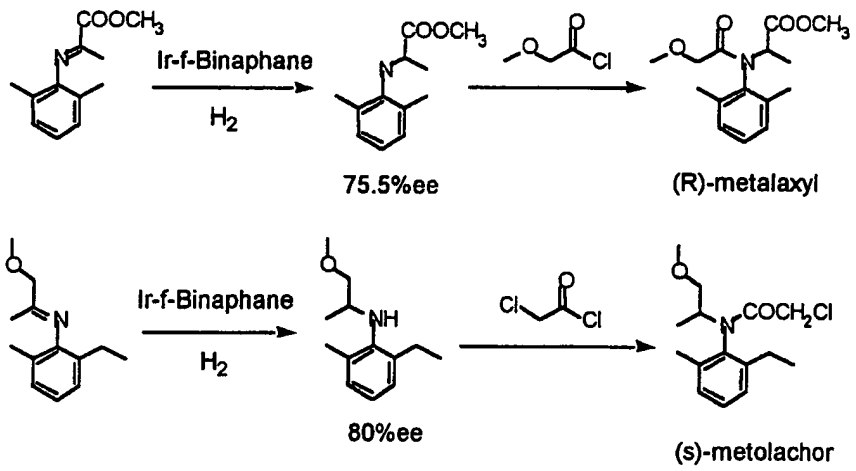
N-(2'-Methoxy-6'-methylphenyl)-1-phenylethylamine (7k): ^{1}H NMR ($CDCl_3$, 360MHz) δ7.22-7.14(4H, m, Ar-H), 7.09-7.07(1H, t, Ar-H), 6.69-6.64(1H, t, Ar-H), 6.59-6.53(2H, m, Ar-H), 4.44-4.39(m, 1H, CH), 3.83(1H, b, NH), 3.63(3H, s, OCH_3), 2.16(3H, s, $ArCH_3$), 1.39-1.37(3H, d, J=6.73Hz, CH_3). ^{13}C NMR ($CDCl_3$, 360MHz) δ151.77, 146.14, 136.24, 129.81, 128.63, 127.31, 126.59, 124.01, 121.44, 108.98, 56.67, 56.13, 23.90, 19.33ppm.

N-(2'-Methoxy-6'-methylphenyl)-1-naphthylethylamine (71): ^{1}H NMR ($CDCl_3$, 300MHz) δ8.08-8.05(1H, d, J=8.06Hz, Ar-H), 7.74-7.71(1H, d, J=7.49Hz, Ar-H), 7.61-7.59(1H, D, J=8.16Hz, Ar-H), 7.54-7.51(1H, d, J=6.84Hz, Ar-H), 7.38-7.30(3H, m, Ar-H), 6.64-6.54(3H, m, Ar-H), 5.39-5.33(1H, m, CH), 4.08(1H, b, NH), 3.64(3H, s, OCH_3), 2.13(3H, s, $ArCH_3$), 1.48-1.46(3H, d, J=6.66Hz, CH_3). ^{13}C NMR($CDCl_3$, 300MHz) δ151.25, 142.46, 136.52, 134.32, 131.42, 129.29, 128.92, 127.62, 126.30, 126.04, 125.76, 124.23, 123.62, 122.86, 120.87, 109.09, 56.17, 52.37, 24.32, 19.61ppm.

General Procedure for deprotection of amines 7(k-l): The N-protected amine **7k/71** was dissolved in a mixture of MeOH/H_2O (4:1). CAN (4eq) was added at 0°C, and the mixture was stirred for 6h at the same temperature. Water was added and the solution was washed with CH_2Cl_2. The aqueous solution was made alkaline by adding 1N NaOH, and then extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed and the residue was subject to chromatography to afford the pure product **8k/81.**

Another potential application of this transformation is the synthesis of chiral agrochemicals. The preparation of (R)-metalaxyl and (S)-metolachor is shown below.

Synthesis of Agrochemicals via Imine Reduction

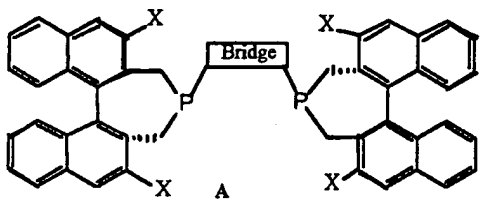


Alternative work-up and isolation procedures are also possible, and will be evident to those skilled in the art.

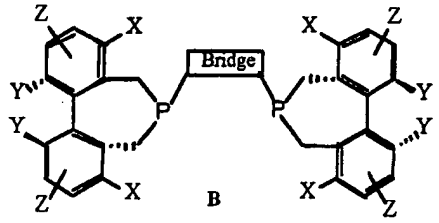
The present invention has been described with particular reference to the preferred embodiments. It should be understood that the foregoing descriptions and examples are only illustrative of the invention. Various alternatives and modifications thereof can be devised by those skilled in the art without departing from the spirit and scope of the present invention. Accordingly, the present invention is intended to embrace all such alternatives, modifications, and variations that fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A ligand selected from the group consisting of compounds represented by A through K:



A



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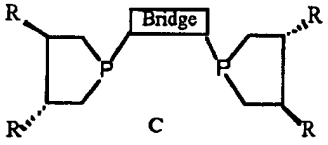

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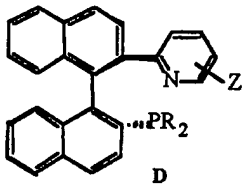

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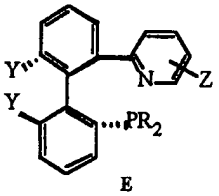

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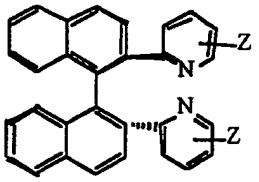

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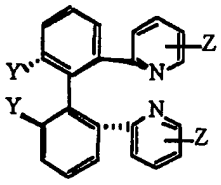

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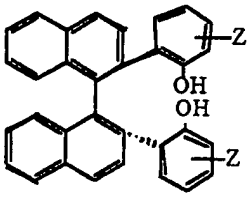

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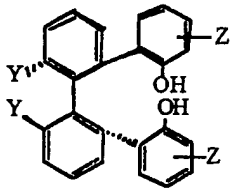

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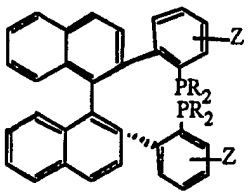

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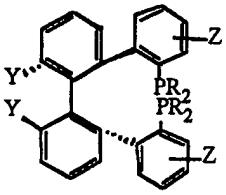


K

wherein the bridge group is selected from the group consisting of: $(CH_2)_n$ wherein n is an integer ranging from 1 to 8, $(CH_2)_nW(CH_2)_m$ wherein n and m are independently an integer ranging from 1 to 8 and W, wherein W is a divalent group selected from the group consisting of: 1,2-divalent phenyl, 2,2'-divalent 1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl, ferrocene, and a substituted derivative thereof; wherein each substituent in said substituted derivative is selected from the group consisting of: aryl, alkyl having 1-8 carbon atoms, F, Cl, Br, I, COOR, SO_3R, PR_3R_2, OR, SR, PR_2, AsR_2, SbR_2, aryloxyl, nitro, NR_2, vinyl, substituted vinyl and a combination thereof, wherein each R is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkaryl and aralkyl; wherein each X is independently selected from the group consisting of: hydrogen, halide, alkyl, aryl, alkoxy, silane, carboxylate and amide; each Y is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, carboxylate and amide; and each Z is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, amide, carboxylate, and a heterocyclic compound.

2. The ligand of claim 1, wherein said heterocyclic compound is selected from the group consisting of: a nitrogen heterocycle, a sulfur heterocycle and an oxygen heterocycle.

3. The ligand of claim 1, wherein said ligand is one of the enantiomers.

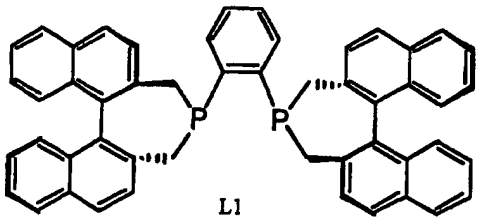
4. The ligand of claim 1, wherein said ligand is a racemic mixture of enantiomers.

5. The ligand of claim 1, wherein said ligand is a non-racemic mixture of enantiomers.

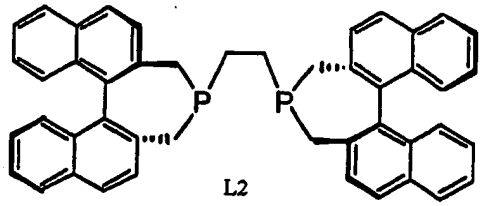
6. The ligand of claim 1, having an optical purity of at least 85% ee.

7. The ligand of claim 1, having an optical purity of at least 95% ee.

8. The ligand of claim 1, wherein said ligand is selected from the group consisting of:



L1



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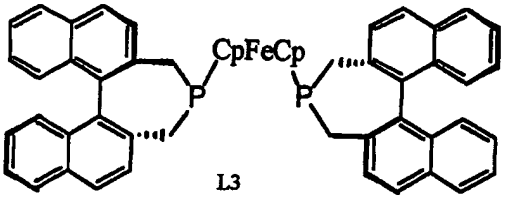

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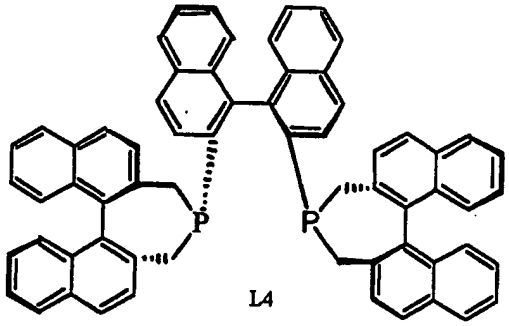

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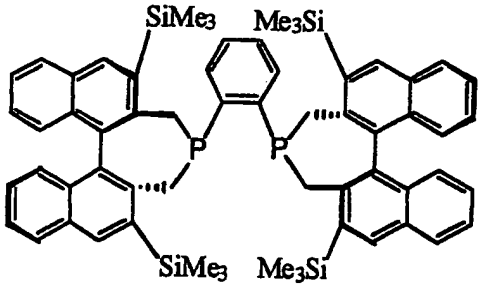

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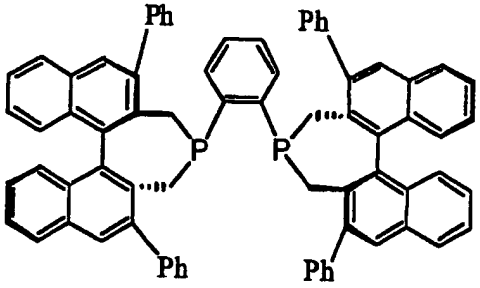

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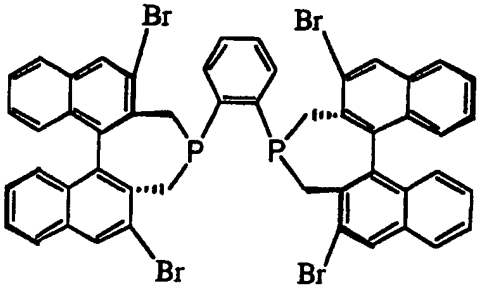

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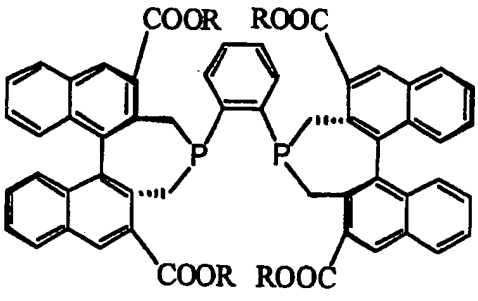

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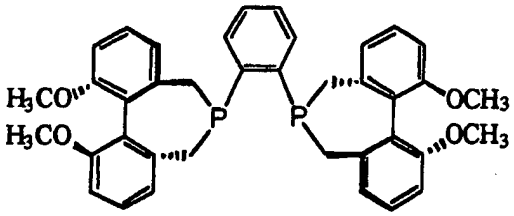

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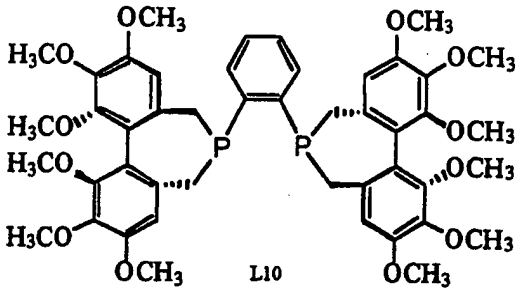

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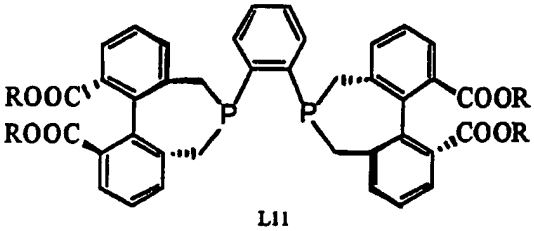

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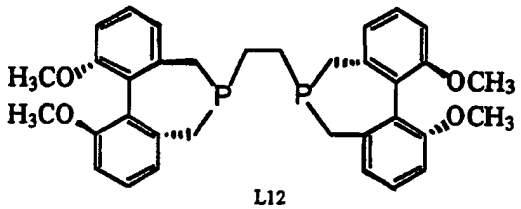

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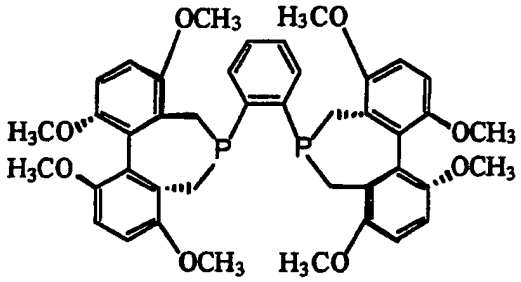

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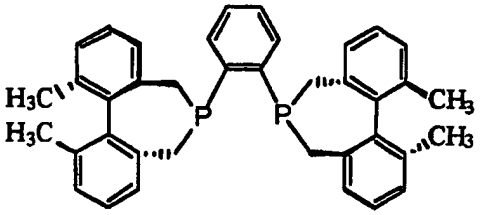

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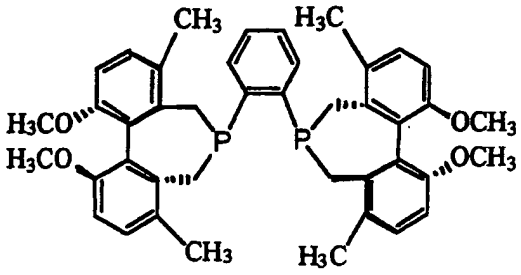

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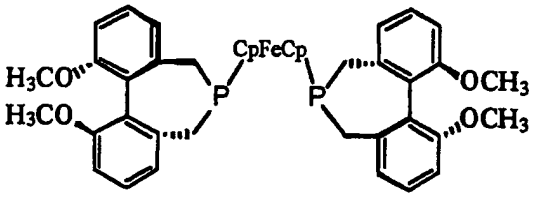

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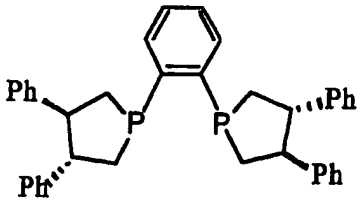

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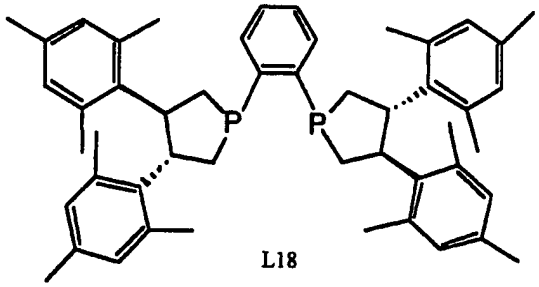

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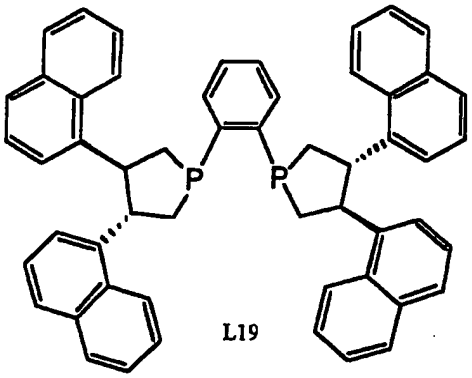

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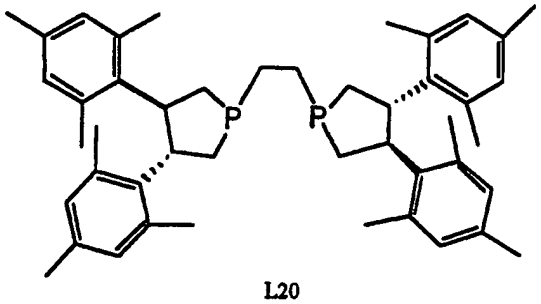

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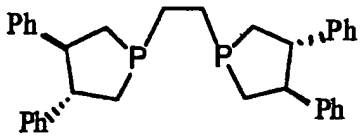

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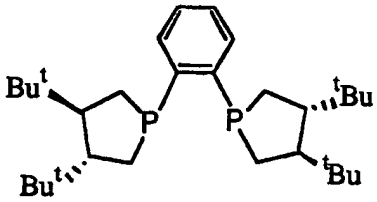

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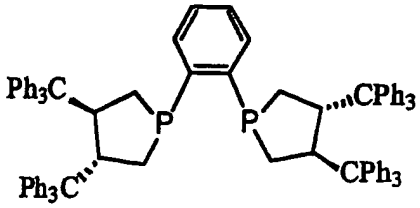

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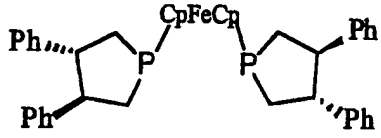

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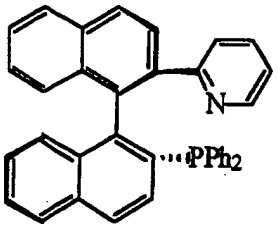

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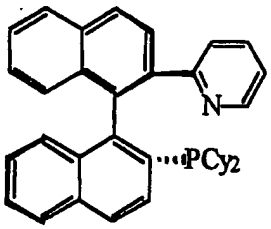

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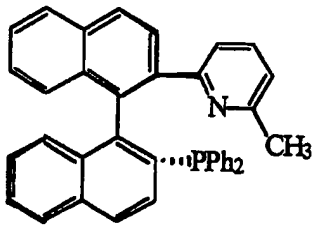

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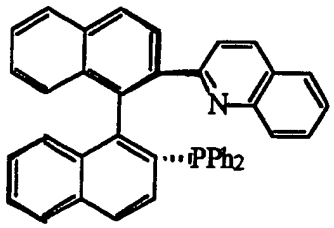

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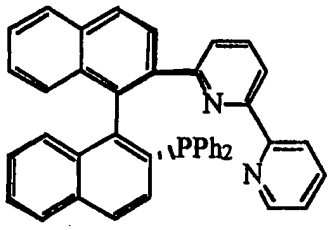

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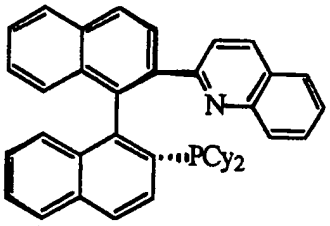

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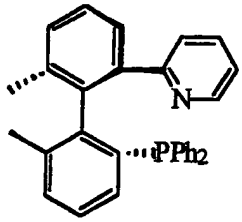

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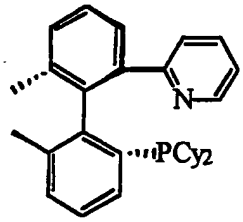

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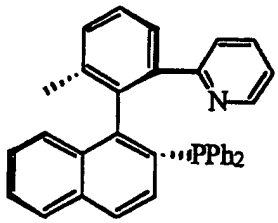

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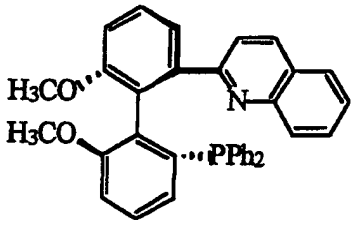

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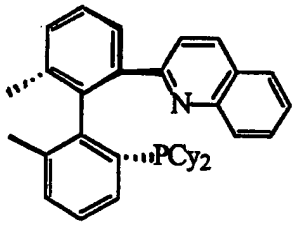

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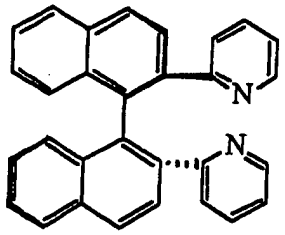

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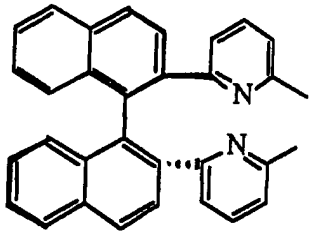

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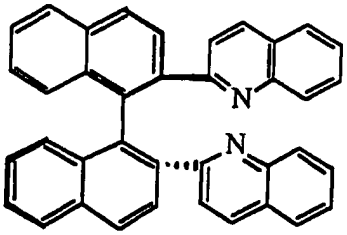

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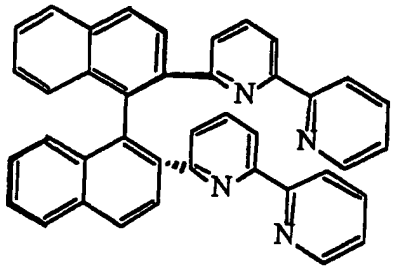

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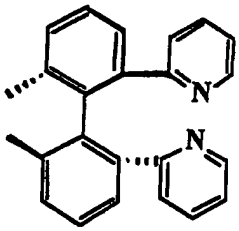

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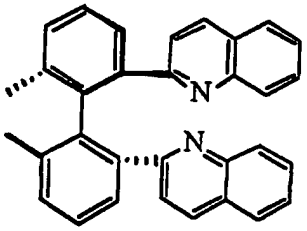

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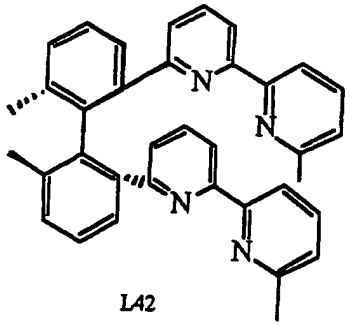

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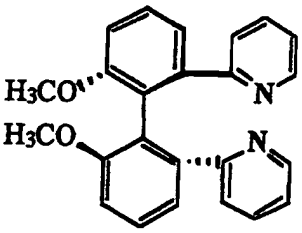

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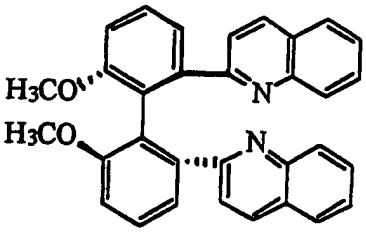

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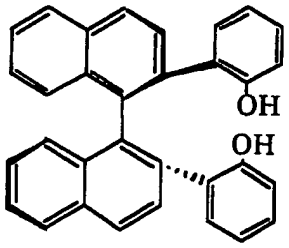

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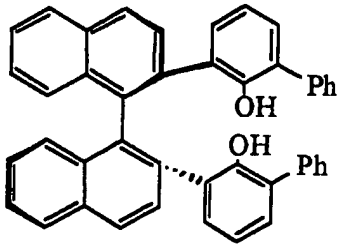

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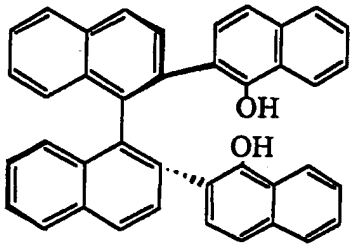

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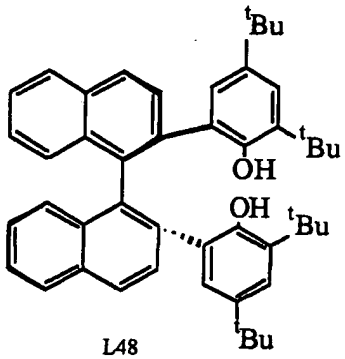

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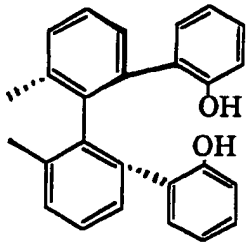

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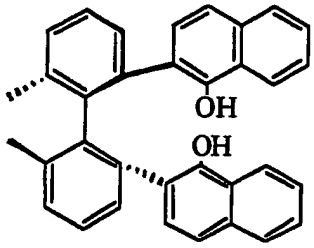

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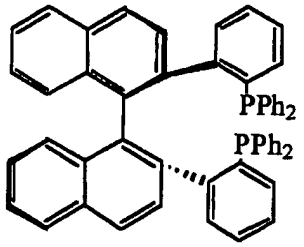

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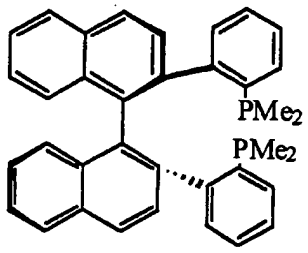

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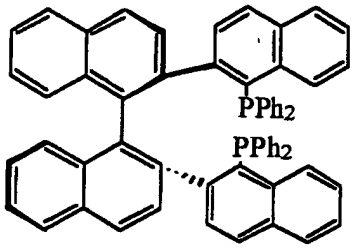

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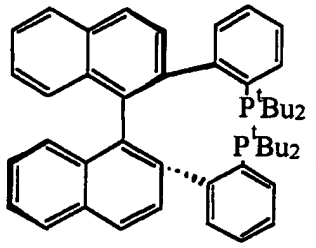

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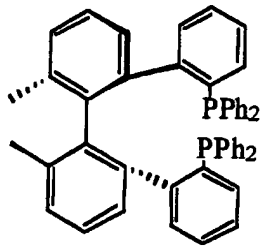

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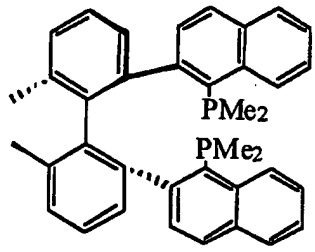
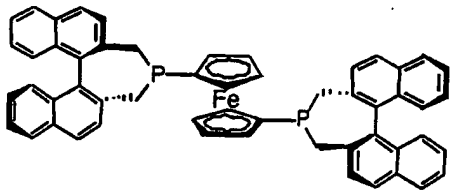


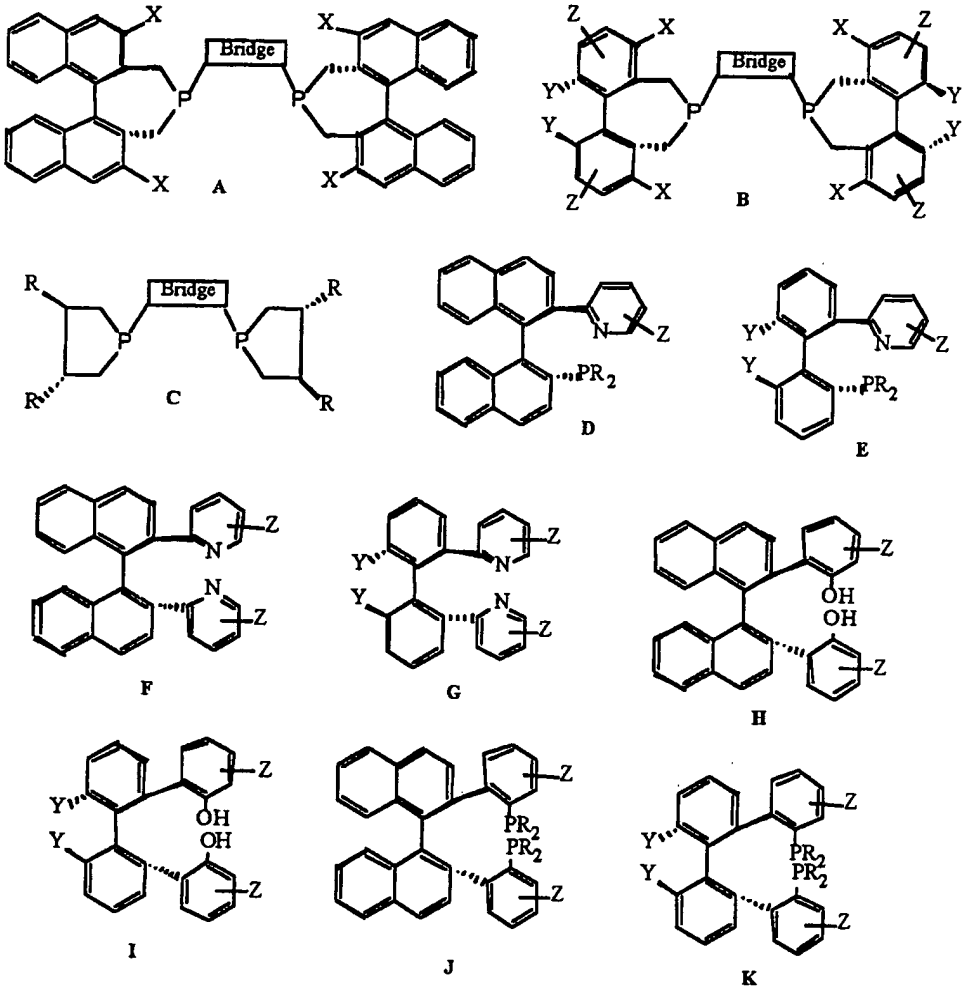
L56

9. The ligand of claim 1, wherein said ligand is a chiral f-binaphane.

10. The ligand of claim 9, wherein said ligand is (*R*,*R*)-f-binaphane represented by the formula:



11. A catalyst prepared by a process comprising: contacting a transition metal salt, or a complex thereof, and a ligand selected from the group consisting of compounds represented by A through K:



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wherein the bridge group is selected from the group consisting of: $(CH_2)_n$ wherein n is an integer ranging from 1 to 8, $(CH_2)_nW(CH_2)_m$ wherein n and m are independently an integer ranging from 1 to 8 and W, wherein W is a divalent group selected from the group consisting of: 1,2-divalent phenyl, 2,2'-divalent 1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl, ferrocene, and a substituted derivative thereof; wherein each substituent in said substituted derivative is selected from the group consisting of: aryl, alkyl having 1-8 carbon atoms, F, Cl, Br, I, COOR, SO_3R, PR_3R_2, OR, SR, PR_2, AsR_2, SbR_2, aryloxyl, nitro, NR_2, vinyl, substituted vinyl and a combination thereof, wherein each R is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkaryl and aralkyl; wherein each X is independently selected from the group consisting of: hydrogen, halide, alkyl, aryl, alkoxy, silane, carboxylate and amide; each Y is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, carboxylate and amide; and each Z is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, amide, carboxylate, and a heterocyclic compound.

12. The catalyst of claim 11, wherein said catalyst is one of the enantiomers.

13. The catalyst of claim 11, wherein said catalyst is a racemic mixture of enantiomers.

14. The catalyst of claim 11, wherein said catalyst is a non-racemic mixture of enantiomers.

15. The catalyst of claim 11, having an optical purity of at least 95% ee.

16. The catalyst of claim 11, wherein said transition metal is selected from the group consisting of: Pt, Pd, Rh, Ru, Ir, Cu, Ni, Mo, Ti, V, Re and Mn.

17. The catalyst of claim 16, wherein said transition metal salt, or complex thereof, is selected from the group consisting of: $PtCl_2$; $Pd_2(DBA)_3$; $Pd(OAc)_2$; $PdCl_2(RCN)_2$; $[Pd(allyl)Cl]_2$; $[Rh(COD)Cl]_2$; $[Rh(COD)_2]X$; $Rh(acac)(CO)_2$; $Rh(ethylene)_2(acac)$; $Rh(CO)_2Cl_2$; $Ru(RCOO)_2(diphosphine)$; $Ru(methylallyl)_2(diphosphine)$; $Ru(aryl\ group)X_2(diphosphine)$; $RuCl_2(COD)$; $[Rh(COD)_2]X$; $RuX_2(diphosphine)$; $RuCl_2(=CHR)(PR'_3)_2$; $Ru(ArH)Cl_2$; $Ru(COD)(methylallyl)_2$; $[Ir(COD)_2Cl]_2$; $[Ir(COD)_2]X$; $Cu(OTf)$; $Cu(OTf)_2$; $Cu(Ar)X$; CuX; NiX_2; $Ni(COD)_2$; $MoO_2(acac)_2$; $Ti(OiPr)_4$; $VO(acac)_2$; $MeReO_3$; MnX_2 and $Mn(acac)_2$; wherein each R and R' is independently selected from the group consisting of: alkyl or aryl; Ar is an aryl group; and X is a counteranion.

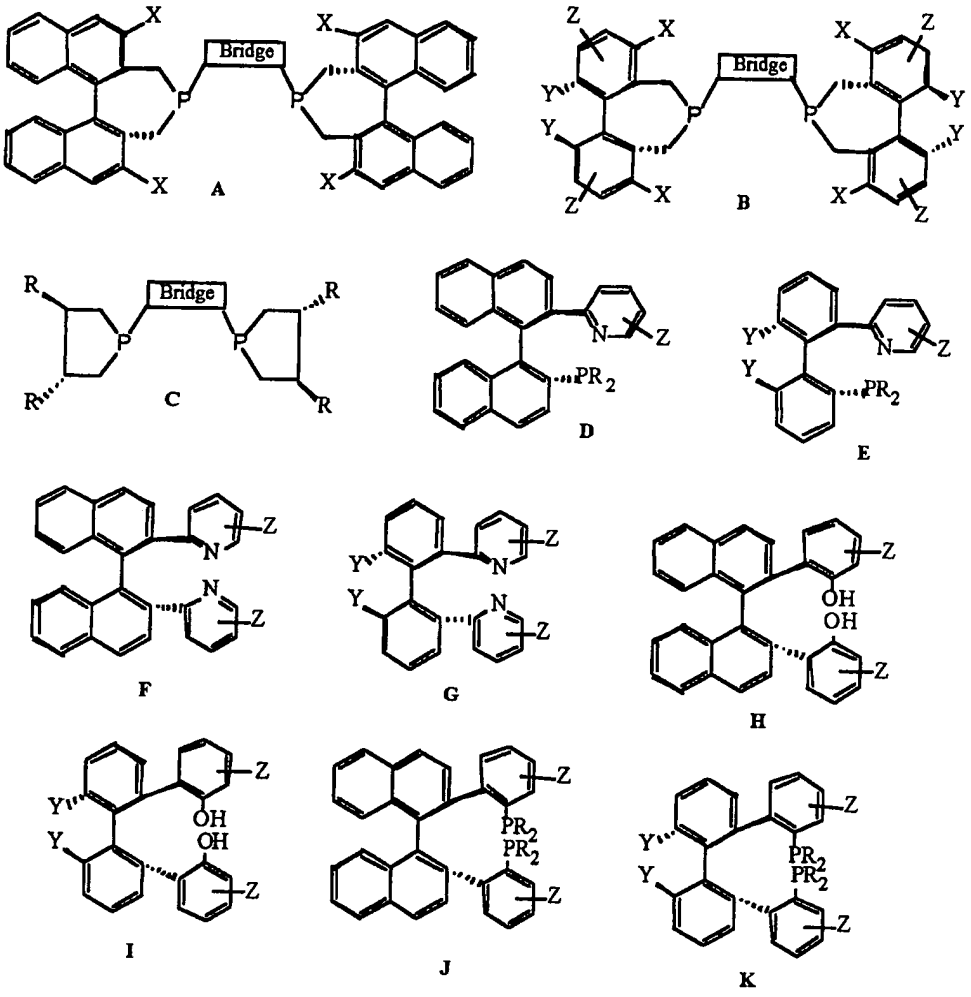
18. The catalyst of claim 11, wherein said counteranion X is selected from the group consisting of: halogen, BF_4, ClO_4, SbF_6, CF_3SO_3 and a mixture thereof.

19. The catalyst of claim 11, wherein said ligand is chiral f-binaphane and said transition metal is Ir.

20. The catalyst of claim 11, prepared in situ or as an isolated compound.

21. A process for preparation of an asymmetric compound comprising:

contacting a substrate capable of forming an asymmetric product by an asymmetric reaction and a catalyst prepared by a process comprising: contacting a transition metal salt, or a complex thereof, and a ligand selected from the group consisting of compounds represented by A through K:



wherein the bridge group is selected from the group consisting of: $(CH_2)_n$ wherein n is an integer ranging from 1 to 8, $(CH_2)_nW(CH_2)_m$ wherein n and m are

independently an integer ranging from 1 to 8 and W, wherein W is a divalent group selected from the group consisting of: 1,2-divalent phenyl, 2,2'-divalent 1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl, ferrocene, and a substituted derivative thereof; wherein each substituent in said substituted derivative is selected from the group consisting of: aryl, alkyl having 1-8 carbon atoms, F, Cl, Br, I, COOR, SO_3R, PR_3R_2, OR, SR, PR_2, AsR_2, SbR_2, aryloxyl, nitro, NR_2, vinyl, substituted vinyl and a combination thereof, wherein each R is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkaryl and aralkyl; wherein each X is independently selected from the group consisting of: hydrogen, halide, alkyl, aryl, alkoxy, silane, carboxylate and amide; each Y is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, carboxylate and amide; and each Z is independently selected from the group consisting of: hydrogen, alkyl, aryl, alkoxy, amide, carboxylate, and a heterocyclic compound.

22. The process of claim 21, wherein said asymmetric reaction is selected from the group consisting of: hydrogenation, hydride transfer, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition and epoxidation.

23. The process of claim 21, wherein said asymmetric reaction is hydrogenation; and said substrate is selected from the group consisting of: ethylenically unsaturated compound, imine, ketone, enamine, enamide and vinyl ester.

24. The process of claim 21, wherein said catalyst is an Ir complex of chiral f-binaphane and said asymmetric reaction is hydrogenation of imines to produce a chiral amine.

25. A process for preparing a chiral f-binaphane or a substituted derivative thereof, comprising:

contacting chiral 1,1'-di(chloromethyl)binaphthyl or a substituted derivative thereof and 1,1'-bisphosphinoferrocene or a substituted derivative thereof in the presence of a base and a solvent to produce f-binaphane or a substituted derivative thereof.

26. The process of claim 25, wherein said base is NaH.

27. The process of claim 25, wherein said solvent is tetrahydrofuran is (THF).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/22976

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07C 39/205, 233/66; C07D 213/04; C07F9/50, 58
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/22, 23, 255, 261, 262, 314, 329; 568/8, 8, 12, 17, 706, 707, 716, 717, 718

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

HAWLEY'S CONDENSED CHEMICAL DICTIONARY-TWELFTH EDITION

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 5,648,547 A (REGNAT) 15 July 1997 (15.07.97), see columns 1-2 and examples.	1, 3-5, 8 ---- 21-22
A --- Y	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:119:116906, CHIBA, T. et al, '2,2'-Bis(dicyclohexylphoshphino)-6,6'-dimethyl-1,1'-bipheny(BICHEP)-ruthenium complexes, highly efficient catalysts for asymmetric hydrogenation of carbonyl compounds', Tetrahedron Lett., 34(14) pages 2351-4, August 1993.	11-20, 23 --- 21-22

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 OCTOBER 2000	Date of mailing of the international search report 24 NOV 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN F VOLLANO Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/22976

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A --- Y	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:94:121896, MIYASHITA, A. et al, ' Synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(BINAP), an atropisomeric chiral bis(triaryl)phsohine, and its use in the rodium(i)-catalyzed asymmetric hydrogenation of alpha-(acylamino)acrylic acids', J. Am. Chem. Soc. 102(27) pages 7932-4, 1980.	11-20 ---- 21-23
A --- Y	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:101:171457, MIYASHITA, A. et al, '2-2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). A new atropisomeric bis(triaryl)phosphine. Synthesis and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of alpha-(acylamino)acrylic acids', Tetrahedron 40(8) pages 1245-53, 1984.	11-20, 24-27 ---- 21-23
A	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:130:52214, REETZ, M.T. et al, 'Diphosphonites as highly efficient ligands for enantioselective rhodium-catalyzed hydrogenation', Chem. Commun.(Cambridge) (19) pages 2077-2078, 1998.	1-27
A	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:118:255441, NANDIN DE CARVALHO, H. et al, '2,2',3,3',5,5'-Hexaphenyl-[1,1'-biphenyl]-4,4'-diols as monomer units for redox polymers: synthesis and polymerization strategies', J. Macromol. Sci., Pure Appl. Chem. A30(6-7), pages 385-97, 1993.	1-8
A	Database CAPLUS on STN, Chemical abstracts (Columbus, Ohio, USA), CA:117:48676, BURK, M.J. et al, 'Asymmetric intramolecular hydrosilylation of hydroxy ketones', Tetrahedron Lett. 33(16), pages 2099-102, 1992.	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/22976

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

546/22, 23, 255, 261, 262, 314, 329; 568/8, 8, 12, 17, 706, 707, 716, 717, 718

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CAS ONLINE, EAST, BEILSTEIN

search terms: structure drawing for the different groups, phosphepin, binaphthlyl, ferrocene, phenol, pyridine, phosphine, enantiomer, hydrovinylation, hydrosilylation, Heck, Michael addition, epoxidation.